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MENINGIOMAS WITHIN THE LATERAL VENTRICLE

BY

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Meningiomas within the lateral ventricle of the brain, although rare, are interesting from both clinical and pathological points of view. Diagnosis without special investigation is difficult, because, although most of these tumours produce focal signs, such signs are indistinguishable from those due to more common tumours in the posterior part of the cerebral hemisphere. The benign nature and intraventricular position of the tumour are usually surprise findings. Another aspect of surgical importance is that although these tumours have characteristics which render their total removal easy, operation is often followed by severe and lasting disability, caused by inevitable damage to overlying brain in securing access to the growth. Their interest to pathologists lies in the problem of their origins and the inferences some workers have drawn from a study of their histology.

This paper will describe eight such meningiomas personally observed during the last five years, and will review, especially from the clinical aspect, cases previously recorded.

A note on terminology is necessary at the outset. The term " meningioma within the lateral ventricle " is used here to designate a meningioma either lying free within the ventricle except for its attachment to the choroid plexus, or lying partly in the ventricle and partly embedded in the cerebral hemisphere. Cushing and Eisenhardt (1938) differentiate between these types, calling the former " true plexus meningiomas " and the latter " lateral tumours of the velum, or sub-cortical meningiomas ". However, they agree that at operation it is often difficult to assign a tumour to one of these categories and indeed that a classification into these two types may not be fundamentally correct.

Previously Recorded Cases

About 50 histologically proven examples of meningioma within the lateral ventricle have been described, 20 by Cushing and Eisenhardt (1938), 22 by Abbott and Courville (1942), and more recently cases have been recorded by Rasmussen (1941), Knight (1949), Huber (1950), and Chavany, Bonduelle, and Guiot (1952).

The average age of the patients was 32 years, the youngest being $3\frac{1}{2}$ years (Gardner and Turner, 1938) and the eldest 65 years (Jefferson and Jackson, 1938). Females were affected more commonly than males in the ratio of 7 to 3.

Symptoms and Signs.—As with meningiomas elsewhere the duration of symptoms, which varied from a few months to eight years, bore no relation to the probable age of the tumour. The first symptom in the majority of cases was headache and as a rule there were no characteristics to distinguish it from headache due to intracranial tumour elsewhere, although occasionally a severe paroxysmal type was recorded (Campbell and Whitfield, 1940). Papilloedema was nearly always present.

Contralateral sensory or motor impairment was recorded in about 70% of cases and usually was not severe. Epileptic fits were rarely described and rarely had localizing value, although one of the patients described by Busch (1939) had had epileptic fits with a visual aura in the blind homonymous field for four years before headache began. Uncinate attacks were described by Love (1935). Homonymous hemianopia, involving mainly lower quadrants and sparing the macula, was described in 60% of cases, whereas visual hallucinations in the blind fields were rare, e.g., Fincher (1934). Dysphasia or dyslexia was only occasionally evident before operation.

Paraesthesiae, paroxysmal or continuous, in the trigeminal area on the same side as the tumour were occasionally noted, but objective evidence of sensory impairment was very rare ; a case with depressed corneal sensation on the same side as the tumour was described by Woolsey and Klemme (1941).

Mental changes were often recorded, one of the

most striking examples being that of Gross (1939).

Signs suggestive of a cerebellar lesion, e.g., ataxia and nystagmus, were noted in about one quarter of the cases, the ataxia being always on the side opposite to the tumour.

Diagnosis.—By clinical examination alone the furthest step ever made was to locate a space-occupying lesion in the appropriate part of one cerebral hemisphere. Its position within the ventricle was never suggested at this stage.

Plain radiographs of the skull sometimes showed calcification within the tumour, e.g., Cohen (1941), but usually ventriculography followed by craniotomy was the method of diagnosis.

On the few occasions when carotid arteriography was used, it merely indicated a mass causing displacement of middle and anterior cerebral vessels. Ameli (1952) has described a case in which the tumour was shown by vertebral arteriography.

Position, Size, and Shape of Tumour.—In 64% of cases the tumours were on the left side, this being especially common in females. The tumour was usually confined to one lateral ventricle, expanding the trigone, having prolongations of variable size forwards into the body and inferior horn and frequently extending into parietal white matter to within 2 cm. of the cortex. The first case described by Busch (1939), which was approached through the frontal horn, showed a small extension of the tumour through the foramen of Monro into the third ventricle, and Busch later found the same feature in two other tumours approached through the parietal lobe.

The weights of the tumours varied from about 20 g. to 340 g. (Hoen quoted by Cushing).

Histology.—Abbott and Courville (1942) observed that all except one of the tumours recorded before 1942 had been called fibroblastic and this description applies to most of the tumours recorded since then. Cushing and Eisenhardt (1938), in differentiating between true plexus meningiomas and lateral tumours of the velum, describe the former as being more highly psammomatous than the latter.

Methods of Removal

In nearly all cases the tumour was approached through the parieto-occipital cortex and white matter, which were either incised or removed. Occasionally, e.g., Busch Case I (1939), the tumour was lying sufficiently far forwards in the ventricle for it to be approached through the frontal lobe.

Results of Operation.—Considered in terms of operative mortality and completeness of removal of the tumours, the results were excellent, but, as most of the tumours were in the left hemisphere, permanent disability of speech was often severe.

Immediate post-operative increase of speech disturbance and hemiparesis always occurred but the latter usually disappeared in the ensuing weeks. Epileptic fits were often recorded. A permanent homonymous field defect was noted when the approach was through the parietal lobe.

The Present Series

The series reported here consists of eight cases.

Case 1.—E. M., a man aged 33, a labourer, was admitted to the National Hospital (No. 10074) in May, 1948, under Dr. F. M. R. Walshe and transferred to Mr. Julian Taylor.

His main complaints were visual deterioration and headache for about two and a half years. The visual changes consisted of blurred central vision and the development of a right-sided field defect. Headache, which was mild and bifrontal, had occurred almost every morning for two years, remaining each time for about two hours and then gradually disappearing. He had had no facial paraesthesiae, no disturbance of speech, and no weakness of the limbs.

On examination the abnormal signs were bilateral anosmia (probably due to chronic catarrh), corrected visual acuity of 6/24 right and 6/36 left and an incongruous right homonymous hemianopia, complete in the lower and partial in the upper quadrants with macular sparing. The nasal margins of both optic discs were blurred but assessment was difficult because of myopia. There was no trigeminal sensory loss, no facial weakness and no motor, reflex, or sensory abnormalities in the limbs or trunk.

Straight radiographs of the skull showed erosion of the dorsum sella. An E.E.G. recorded low-voltage waves of about 2 per second from the left mid-temporal region.

At ventriculography through biparietal burr-holes, only the right ventricle was entered. On the left side at a depth of 3 cm. firm tumour was encountered, which biopsy showed to be a meningioma. The films, which were of little value because no air passed into the left ventricle, showed merely a considerable shift of the right and third ventricles to the right. The protein content of the right ventricular fluid was normal. Left carotid arteriography showed displacement of the anterior cerebral artery to the right, and, in the lateral view, elevation of the middle cerebral vessels. No vessels within the tumour were seen but the anterior choroidal artery was abnormally large and ended posteriorly in a small tangle of vessels.

Craniotomy was then performed under local anaesthesia and the left parieto-occipital area exposed.

Tumour was seen at a depth of 1 cm. after making a vertical cortical incision about 3 cm. long in the posterior parietal region. Attempts were made to remove its centre with the diathermy loop, but this proved difficult and it was eventually delivered intact.

The day after operation there was severe speech disturbance but no gross weakness of the face or limbs. One month later there was still considerable dysphasia and dyslexia and also slight weakness of the right foot and hand, but no postural sense loss or astereognosis. The right homonymous hemianopia was now complete in the upper and lower quadrants, the maculae being spared. Visual acuity had improved to 6/18 right and left.

Two years after operation, although he denied speech difficulty, there was obvious nominal dysphasia, and comprehension of written words was poor. The hemianopia was unchanged. He was considered fit to resume his previous work as a labourer although he had not then done so.

The main mass of tumour measured 7 by 5·5 by 5 cm. and weighed 134·5 g. Choroid plexus was adherent to its surface for a distance of 4 cm. Histologically it was a fibrous type of meningioma, composed mostly of bundles of spindle-shaped cells, which in some parts formed whorls. Areas of meningothelial cells were scanty and no psammoma bodies were seen (Fig. 1).

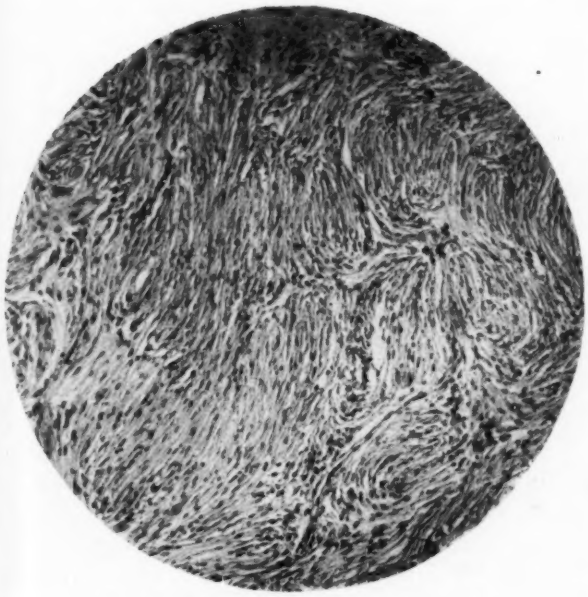

FIG. 1.—Case 1 : Section of tumour. × 80.

This case was unusual in that the only focal sign before operation was the homonymous field defect.

Case 2.—R. T., a man aged 41, a wood machinist, was admitted to the National Hospital (No. 20617) in December, 1949, under Dr. S. P. Meadows and transferred to Mr. Harvey Jackson.

His main complaints were headache and visual disturbance.

The headache began six months previously, was at first frontal, later occipito-frontal, occurred about twice a week and although usually only a dull ache, on about four occasions had been very severe. For the two or three weeks before admission he had been free of headache.

The visual disturbance was the complaint for which he sought advice because it interfered with his work. He described it as a " kink " or " zigzag " at the point of fixation, especially troublesome when looking at a line of print or a vertical line. There was no suggestion of hemianopia. In a similar way to the headache this symptom had also become less obvious for the two or three weeks before admission.

In addition to these main symptoms he complained also that during the attacks of vomiting accompanying severe headache there was a sensation that his surroundings were rotating, in no particular direction, and lasting for a few seconds only.

There was no history of mental change, of impaired visual acuity, or of sensory or motor symptoms in trunk or limbs. He was right handed.

On examination the abnormal signs were bilateral papilloedema greater on the left, irregular nystagmus on conjugate lateral gaze especially to the left, slight weakness of the right leg, slight ataxia in the finger-nose test on both sides, more on the left, slight bilateral ataxia in the heel-knee test, bilateral extensor plantar responses, slight unsteadiness of gait especially when turning rapidly, and postural sense impairment in the right hallux. There was no field defect, visual acuity was 6/12 on both sides, and there was no evidence of mental deterioration, dysphasia, or dyslexia.

Radiographs of the skull were normal.

An E.E.G. showed waves of 4 to 6 per second which, although bilateral, were more prominent on the left side, and also 1 to 2 per second waves which were almost entirely left sided, with a maximal focus in the anterior temporal region.

Ventriculography through biparietal burr-holes showed a shift of the lateral and third ventricles to the right with dilatation of the left occipital and temporal horns. The tumour was demarcated by crescentic shadows in the posterior part of the body of the left ventricle and anterior part of the occipital horn. Cerebrospinal fluid from the right ventricle contained 15 mg. of protein per 100 ml. ; that from the left. 100 mg.

A burr-hole was then made above the upper temporal crest and about 3 cm. behind the coronal suture. Needling directly inwards encountered very firm resistance beyond which a cavity was entered and 10 ml. of cloudy-white fluid aspirated. Needling in other directions established that the mass was not very large. No biopsy was taken. (In retrospect it seems likely that the needle had penetrated through the tumour, although it was never decided whence the opalescent fluid had come.)

A large left fronto-temporal flap was later elevated and an attempt made to reach the tumour through a

vertical cortical incision in the frontal lobe, but without success.

Following this operation the patient had a right hemiplegia, aphasia, and a right homonymous hemianopia. Three weeks later the hemiplegia and aphasia had considerably improved and he was able to converse hesitantly. The field defect remained unchanged.

After a second ventriculography, a further needle biopsy was attempted. Although none of the tumour could be withdrawn, the impression was gained that it was movable.

A second craniotomy was then undertaken allowing access to the parieto-occipital region. A vertical cortical incision on the convexity was made and deepened until the ventricle was entered and the firm, nobbly tumour exposed, lying mainly in the expanded trigone with a short extension forwards into the body of the ventricle. Traction sutures were inserted and, as the mass was delivered, its main blood supply, from the choroid plexus on its anterior and medial aspects, was divided.

This procedure considerably increased the dysphasia and hemiparesis. Twelve days after operation he became drowsy and vomited repeatedly. Tapping of the left ventricle allowed 35 ml. of old blood to escape under pressure, and after another tap later in the day when 12 ml. more were removed, he gradually improved.

Three weeks after operation there was no weakness of the limbs and only slight facial weakness. Deep reflexes were brisker on the right side and the right plantar response was extensor. The right half of the trunk and the right limbs showed tactile inattention without impairment of pain or touch sensation. Stereognosis could not be tested. He was dysphasic and unable to read, although he could understand simple spoken speech and was able to utter simple phrases. The field defect remained unchanged.

After five months of speech therapy he was able to read and speak simple sentences. About this time he began having fits, usually only right sided but sometimes generalized.

He was last heard of a year after operation. He was still having occasional fits, but had resumed his previous work as a joiner. Dysphasia was still obvious, the field defect unchanged, the right tendon reflexes were still the brisker and the right plantar response extensor.

The tumour, which measured 5 by 4 by 3·5 cm. and weighed 45·5 g., showed the same cellular structure as that of Case 1, except that islands of meningothelial cells were more numerous and occasional psammoma bodies were seen.

The outstanding feature of this case was the difficulty in deciding, by clinical examination alone, whether the tumour was above or below the tentorium. In fact it was the E.E.G. which gave the first real lead.

Another feature of interest was the onset of a complete homonymous hemianopia after an attempted transfrontal approach.

Case 3.—M. E., a woman aged 51, a housewife, was admitted to the National Hospital (No. 7812) in January, 1948, and again in January, 1950, under Sir Charles Symonds and transferred to Mr. Wylie McKissock.

Her main complaints were headache for one year and weakness of the right limbs for a few weeks.

The headache was always bifrontal, not more on one side than the other, present when wakening in the mornings and usually recurring in the evenings, was severe for only about 15 minutes at the beginning of each attack, and then gradually disappeared over the next few hours.

Weakness of the right hand had developed very gradually over the previous three weeks and of the right foot over a period of six weeks, the weakness slowly spreading to involve more proximal muscles. She was, however, still able to walk and to grip objects with the right hand.

There had been no visual disturbance, no fits, and no facial paraesthesiae. She was right handed.

On examination the abnormal signs were moderate nominal dysphasia, early swelling of both optic discs, visual inattention in the right half fields, slight right facial weakness, slight weakness of the right arm and leg with increased deep reflexes and impaired postural sense on this side.

There was no trigeminal sensory loss and visual acuity was 6/24 on both sides.

Lumbar cerebrospinal fluid pressure was 205 mm. and protein 55 mg. per 100 ml.

Routine radiographs of the skull showed erosion of the posterior clinoids.

An E.E.G. recorded slow waves of 1 to 4 per second from a wide area in the left parietal region.

Ventriculography through a right parietal burr-hole showed displacement of the lateral and third ventricles to the right and a filling defect in the region of the left trigone some 6·5 cm. in antero-posterior diameter. The left anterior horn was smaller than the right. The protein content of the right ventricular fluid was normal.

Biopsy showed the tumour to be a meningioma.

Craniotomy was subsequently performed and the left parietal cortex exposed. A vertical cortical incision about 3 cm. long was made in the posterior parietal region and deepened until soft vascular tumour was exposed, much of which was removed with the sucker. The wound was then closed.

This procedure produced a slight increase in the previously recorded signs. Dysphasia was a little more obvious and the right plantar response became extensor. The field defect, however, remained only relative.

Deep *x*-ray therapy was instituted and after this there was considerable improvement in the patient's general and mental state. Physical signs remained unchanged except that there was now a complete right homonymous hemianopia.

During the next six months her general condition continued to improve a little, but at the end of this period morning vomiting began and she was readmitted. During the first few days in hospital vomiting continued

and severe frontal headache appeared. Physical signs remained unchanged.

A second craniotomy, two years after the first, was then performed using the previous bone flap. A similar vertical cortical incision was made in the posterior parietal region and deepened until tumour was seen. After some separation, the dilated temporal horn was entered and choroid plexus identified. It was adherent to the tumour in the posterior part of the temporal horn and was divided. The posterior part of the tumour, apparently blocking completely the occipital horn, was removed, mostly by suction. There remained the main mass of tumour in the expanded trigone, with an extension forward into the posterior part of the body of the ventricle. Here again plexus was attached and was divided to enable delivery of this remaining mass.

The operation produced temporary increase of the dysphasia and limb weakness, but a month later the patient was able to converse hesitantly and there was only slight weakness of the right arm and leg. There was, however, grossly impaired postural sense in these limbs and a complete right homonymous hemianopia.

During the 18 months following the second operation there was gradual improvement, but the slight right-sided weakness, the gross cortical sensory loss, the field defect, and the now only slight disturbance of speech and reading remained.

The portion of tumour removed *en masse* at the second operation weighed 27·5 g. and measured 4·5 by 4 by 3 cm. Its histological structure was the same as the original biopsy, namely, masses of closely packed cells, most of which were rounded, but some were elongated, and with indistinct cell boundaries. In some areas streaming of the cells was apparent and elsewhere poorly formed whorls. There was a well-defined collagenous capsule but within the tumour only a little fibrous stroma and no psammoma bodies (Fig. 2).

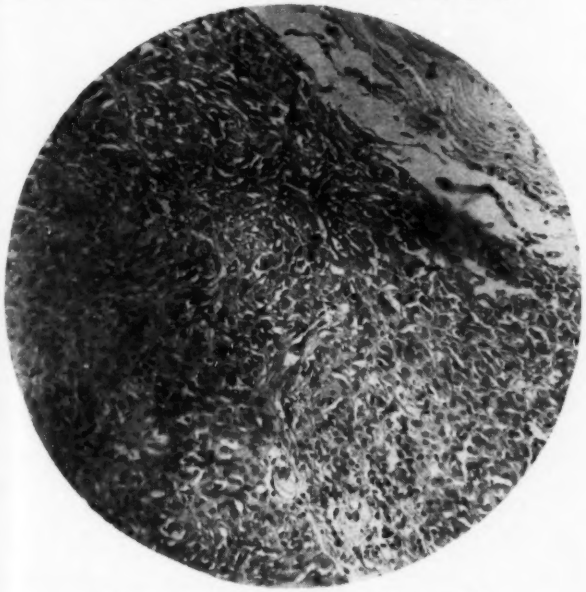

FIG. 2.—Case 3 : Section of tumour. × 100.

The microscopic appearance of the tumour was the most noteworthy feature of this case. It was the only truly syncytial meningioma in the series.

Case 4.—J. M., a girl aged 15, a jewellery polisher, was admitted to the National Hospital (No. 22139) in February, 1950, under Dr. Macdonald Critchley and transferred to Mr. Harvey Jackson.

Her main complaints were headache and weakness of the left limbs. Headache began nine months previously, when, after being in the sunshine, she had a severe, thumping ache above the eyes. This disappeared after a few hours only to return the following day and nearly every subsequent day. Usually it wakened her in the mornings and lasted for about half an hour, and at the time of admission came on later in the day as well, again lasting for only a short time.

About four weeks before admission she began dropping objects from the left hand and she thought the strength of the limb as a whole was reduced. About the same time she began dragging the left foot, but this improved and when in hospital she thought the limb normal ; indeed, she had cycled 60 miles only eight days before.

Also, for about four weeks, usually when washing her face, she had frequently experienced " a twitching feeling " on the right side from eye to chin, although not accompanied by actual movement. Her mother described one of these attacks as occurring at the time of a very severe headache and associated with transient severe weakness of the left hand. The patient was right handed.

On examination the abnormal signs were mild intellectual impairment, severe chronic papilloedema, complete left homonymous hemianopia with macular sparing, moderate weakness of the left arm, slight weakness of the left leg, brisker deep reflexes on the left with an equivocal left plantar response (the right being obviously flexor) gross impairment of postural sense, two-point discrimination and stereognosis in left hand and foot, with inattention on the left limbs to bilateral pain and touch stimuli.

Visual acuity was 6/6 on both sides, there was no facial weakness, and no trigeminal sensory loss.

Straight radiographs of the skull showed erosion of the posterior clinoids.

An E.E.G. recorded high-voltage waves of 1 to 3 per second arising from the right temporo-parietal region.

Ventriculography through biparietal burr-holes showed displacement of the ventricles to the left with dilatation of the right frontal and temporal horns. A mass, some 7·5 cm. in diameter, was outlined in the region of the right trigone. Cerebrospinal fluid from the left ventricle contained a normal amount of protein, that from the right about 45 mg. per 100 ml.

At operation, a curved cortical incision in the right superior temporal convolution and adjacent part of the lower parietal area was deepened until the ventricle was entered and the smooth-walled tumour exposed. After preliminary scalloping, and division of the main blood supply passing into its antero-lateral surface, the tumour was delivered intact.

Following this procedure there was no increase in the hemiparesis and three weeks later the weakness of the left arm and leg noted before operation had disappeared. There was, however, gross sensory impairment in the left limbs although less than before operation. The homonymous hemianopia was at first unchanged but subsequently improved slightly, hand movements being appreciated in the left lower quadrant.

She had her first fit five weeks after operation, and in the next two years had infrequent left-sided motor and sensory attacks, some with loss of consciousness. Nevertheless she was able to work.

The tumour weighed 160 g. and measured 8·3 by 6·5 by 5·5 cm. Histologically it was composed of bundles and whorls of spindle cells with numerous islands of more rounded cells. No psammoma bodies were seen.

This was the first case in the series in which trigeminal paraesthesiae were noted.

Case 5.—V. P., a woman aged 35, a housewife, was admitted to the Leeds General Infirmary in March, 1950, under Mr. W. R. Henderson.

Her main complaints were headache and blurring of vision for about two years. The headaches were always generalized, usually on wakening, and had become more frequent and severe in the few weeks before admission.

In addition to the gradual deterioration of central vision beginning two years previously, she had had during this period attacks of diplopia each lasting for a few seconds and frequent visual blackouts, during which she was unable to see anything.

A few weeks before admission there had been an attack of unconsciousness, apparently without convulsion.

She had had no facial paraesthesiae and no speech disturbance. She had been unable to smell for about five years and had been deaf in the left ear for many years, following a childhood infection. She was right handed.

Eighteen months before, examination elsewhere had shown bilateral papilloedema, visual acuity of 6/36 in each eye, and evidence of a right lower quadrantic homonymous hemianopia.

On examination at the time of admission the abnormal signs were bilateral anosmia, bilateral secondary optic atrophy more advanced in the right eye which was blind, and unsustained nystagmus on gaze to right. Vision in the left eye varied from time to time, because although she could apparently feed herself she denied better vision than perception of light. The visual field of the left eye, so far as could be tested, was full.

There was no trigeminal sensory loss, no facial weakness, no motor, reflex, or sensory changes in the limbs or trunk and no speech disturbance.

Lumbar C.S.F. protein was 43 mg. per 100 ml.

An E.E.G. recorded slow waves arising in the left temporo-occipital region.

Radiographs showed faint speckled calcification over an area some 3 cm. in diameter deep in the left mid-parietal region.

Left carotid arteriography showed stretching of the terminal middle cerebral vessels, as if from a subcortical mass, but no vessels within the tumour. The posterior cerebral artery did not fill but it was noted that the anterior choroidal artery was larger than normal and ended in a tuft of vessels below and in front of the area of calcification.

Following this a burr-hole was made on the left side and what was apparently a dilated temporal horn tapped. During the next few days there was a remarkable and unexpected improvement of vision to J.1 left and J.18 right. Further estimation of visual fields was now possible, and no defect was found.

Ventriculography through biparietal burr-holes demonstrated a smooth filling defect about 3·5 cm. in diameter in the region of the left trigone, corresponding to the area of calcification. There was considerable shift of the lateral and third ventricles to the right with dilatation of the left temporal and posterior horns. The left anterior horn was smaller than the right. Unfortunately the ventricular fluids were not examined chemically.

Craniotomy was then undertaken allowing access to the left temporo-parietal region, and a cortical incision about 4 cm. long made in a downwards and forwards direction near the posterior end of the exposure. A vascular tumour was found and a biopsy taken, but no attempt was made to remove it at this stage.

This procedure produced an incomplete right homonymous hemianopia but, surprisingly, no motor or sensory loss in the limbs and no speech disturbance.

Vertebral arteriography later demonstrated several large posterior choroidal vessels ascending from the posterior cerebral artery and running on to the surface of the tumour, the size and shape of which was outlined both by encircling vessels and a haze of contrast medium. The normal pattern of the choroid plexus was not seen (Fig. 3).

FIG. 3.—Case 5 : Vertebral arteriogram showing the outline of the tumour. Shows also the cortical incision (dotted).

At the second-stage craniotomy the original bone flap was elevated and the previous cortical incision enlarged in a downwards and backwards direction for 2 cm. from its lower extremity. The site of the incision is shown in Fig. 3. This extension necessitated division of a large

cortical vein running downwards and forwards. The tumour was considered too large to remove intact and about three-quarters of it was sucked away. As the tumour was separated from the wall of the ventricle fluid was released from the temporal horn and the choroid plexus coagulated just behind the foramen of Monro and again in the posterior part of the temporal horn. Between these points plexus was firmly adherent to tumour.

After three weeks she was walking normally and there was no weakness of the right arm or leg. There was, however, slight right facial weakness, gross postural sense impairment in the right fingers (but not in the toes), complete right homonymous hemianopia and severe dysphasia and dyslexia. Visual acuity remained improved.

She was last seen two years after operation when the signs were essentially the same as at the time of her original discharge. The homonymous field defect was complete, there was gross impairment of postural sense in the right hand, obvious dysphasia, although she was able to hold a reasonable conversation, and almost complete alexia.

The portion of tumour removed intact measured 6 by 4 by 3·5 cm. and weighed 45 g. Histological examination showed bundles and whorls of spindle-shaped cells with numerous psammoma bodies and only a few areas of meningothelial cells (Fig. 4).

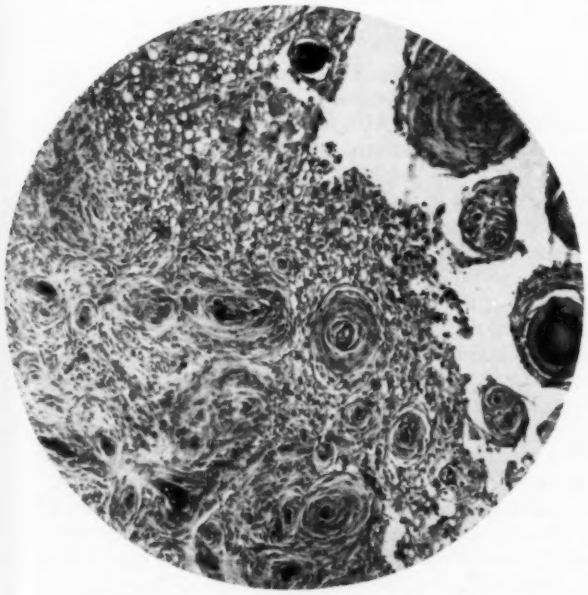

FIG. 4.—Case 5 : Section of tumour. × 80.

Features of interest in this case were (1) the presentation as a case of visual failure due to secondary optic atrophy without focal signs, (2) the calcification seen on straight radiographs, (3) the improvement of vision after tapping the dilated temporal horn, and (4) the demonstration of the tumour by vertebral arteriography.

Case 6.—E. S., a woman aged 35, a housewife, was admitted to Leeds General Infirmary in January, 1951, under Mr. W. R. Henderson.

Her main complaints were headache and tingling on the left side of the face and in the right hand.

She had had headache, which had been called migraine, for at least 10 years, in attacks lasting a day or two, about once a month. It was always frontal, sometimes left, sometimes right, sided. It had disappeared during her first pregnancy 18 months before but had since returned, until at the time of admission it was of daily occurrence.

She had been seen twice, four years previously, because of this headache, but the only abnormal sign found was poor reaction of the right pupil to direct light. On the second of these occasions the headache was much improved and further investigation was not advised.

During the last three months she had had eight or nine attacks, each lasting a minute or so, of tingling on the left side of the face, beginning in the lower lip and spreading into the cheek and temple. They were not associated with headache.

For the same period a similar sensation had occasionally affected all the digits of the right hand. This likewise was independent of headache and also of the tingling in the face.

For a few weeks she had noticed blurring of vision. She was right handed.

On examination the abnormal signs were moderate bilateral papilloedema equal on the two sides, a relative right homonymous hemianopia, visual acuity of 6/12 left and 6/24 right, and brisker deep reflexes on the right side.

There was no trigeminal sensory loss, no abnormality of pupillary reflexes, no facial weakness or hemiparesis and no sensory loss on trunk or limbs.

Straight radiographs of the skull showed erosion of the posterior clinoids.

Lumbar C.S.F. pressure was not measured and the fluid contained 66 mg. of protein per 100 ml.

An E.E.G. was abnormal but without slow waves, showing only a less well defined alpha rhythm on the left.

Left carotid arteriography, at which unfortunately only lateral films were obtained, showed merely stretching of some terminal middle cerebral vessels as if from a deep parietal mass. No vessels within the tumour were seen, the posterior communicating artery was small and the posterior cerebral artery not seen. Definition in these films was poor and the anterior choroidal artery could not, with certainty, be identified.

Ventriculography through biparietal burr-holes showed displacement of the lateral and third ventricles to the right with dilatation of the left temporal and frontal horns. In the trigone region of the left ventricle there was a filling defect about 5 cm. in diameter (Figs. 5 and 6). Cerebrospinal fluid from the left ventricle contained 97 mg. of protein per 100 ml.

Vertebral arteriography showed numerous posterior choroidal arteries ascending from the posterior cerebral artery to form a mass of smaller vessels corresponding to the site of the tumour. The normal pattern of the choroid plexus was not seen.

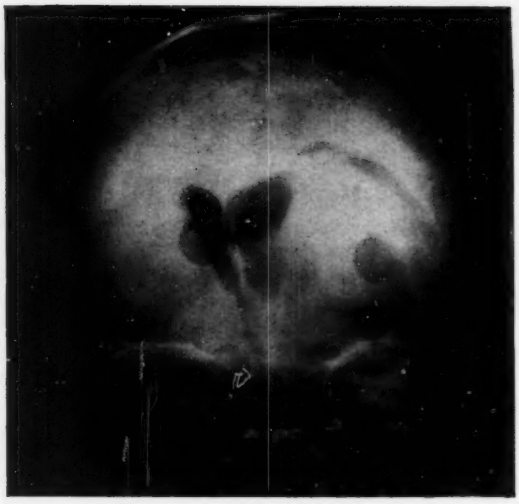

FIG. 5.—Case 6: Antero-posterior ventriculogram showing the dilated temporal horn, air in the elevated trigone, displacement of the ventricles to the right, and dilatation of the anterior part of the body of the left ventricle.

FIG. 6.—Case 6: Lateral ventriculogram showing the tumour (dotted).

At craniotomy, exposing the left parieto-occipital area, the tumour was felt through several needle punctures to be firm and movable and lying about 2 cm. deep to the cortex. A cortical incision some 5 cm. long was made in a postero-anterior direction, beginning posteriorly just medial to the ventriculogram opening, about 3·5 cm. from the mid-line. After deepening the incision and examining the tumour it was considered necessary to enlarge the opening, and this was done, from its anterior extremity, in a downwards direction for 3 cm. After the choroid plexus, entering the antero-inferior aspect of the mass, had been divided, the tumour was removed intact with the aid of traction sutures. A few small vessels on the medial wall of the ventricle then required coagulation and these were the only vascular attachments of the tumour except for the plexus which had previously been divided.

Operation produced a right homonymous hemianopia and an almost complete right hemiplegia. By the tenth day there was no facial weakness and only slight weakness of the arm and leg. Speech slowly improved, but even 14 months after operation it was still impaired, although probably adequate for her needs. Reading, however, was very poor. At this time there was no weakness or postural sense loss in the limbs. The field defect remained complete.

Fits began two days after operation, were at first only right sided, but in the ensuing months were occasionally generalized with loss of consciousness. Suitable medication reduced their frequency to about once every two months.

The tumour weighed 78 g. and measured 6 by 5 by 5 cm. Histological examination showed it to be similar to that of Case 1.

Noteworthy features of this case were the long history of headache and the trigeminal paraesthesiae without objective sensory loss (compare Case 4).

Case 7.—G. S., a man aged 50, a motor mechanic, was admitted to Leeds General Infirmary under Dr. H. Garland in July, 1951, and transferred to Mr. W. R. Henderson's care.

The main features of the history were headache and weakness of the left limbs for a few months.

Headache had started three and a half months before, had become more frequent and severe, and at the time of admission was of daily occurrence. It was always right sided, beginning behind the eye and spreading to the sub-occiput, was present when he wakened in the mornings, disappeared after being up for an hour or so, and was often associated with vomiting.

The left hand had been weak for two and a half months but the weakness had progressed very little. He was still able to grip well but the hand was clumsy for fine movements. For one month he had noticed weakness of the left leg, although this had latterly improved.

During the investigation period in hospital mental confusion appeared and he agreed that this memory was rapidly becoming worse.

There was no history of visual impairment, of fits, or of facial paraesthesiae. He was right handed.

On examination the abnormal signs were complete left homonymous hemianopia, bilateral papilloedema greater on the right, moderate weakness, greater distally, in the left arm and leg and about equal in the two limbs, impaired postural and tactile sense on the left limbs and left side of the trunk, and an extensor plantar response on the left, the right being equivocal.

There was no facial weakness, no trigeminal sensory loss, and no impairment of visual acuity.

Straight radiographs of the skull showed no abnormality.

An E.E.G. recorded continuous low-voltage waves of 2 to 3 per second from the right hemisphere, the maximum disturbance being over the temporal lobe.

A right carotid arteriogram showed moderate displacement of the anterior cerebral artery to the left and,

in the lateral films, slight upwards displacement of middle cerebral vessels and splaying of terminal middle cerebral branches as if from a parietal mass. The posterior cerebral artery was normal. The anterior choroidal artery was larger than normal and ended posteriorly in a tuft of small vessels. No vessels within the tumour were seen.

A right posterior parietal burr-hole was then made and needling towards the trigone encountered from a depth of 2 cm. onwards abnormal resistance from which a biopsy was taken. On several occasions during the next few days he became comatose with a fixed and dilated right pupil but always spontaneously recovered after a few hours.

To obtain more information, vertebral arteriography was done and this showed numerous posterior choroidal vessels ascending from the posterior cerebral artery and apparently stretched over a mass. They did not, however, completely encircle it and no residual haze of contrast was visible. The normal pattern of the choroid plexus was not seen.

Craniotomy was then performed and in the right lower parietal region a horizontal cortical incision about 6 cm. long was made and extended in a curve upwards posteriorly. About a third of the tumour was removed with the diathermy loop and the main mass was then separated from the ventricular wall. A prolongation of the tumour into the temporal horn was seen to be receiving the main vascular supply from the plexus, and when this and a large vein lying posteriorly and passing medially into the choroidal fissure had been divided, the tumour was delivered without bleeding.

The immediate result of the operation was complete hemiplegia which rapidly improved. Three weeks later there was only slight weakness of the left hand and none of the leg, with only slightly impaired postural sense in fingers and toes. The field defect remained unchanged.

About four months after operation he had two generalized fits but had had no more in the ensuing three months. He returned to his previous work, and examination seven months after operation showed no weakness of the left hand and only slight impairment of postural sense in the left fingers.

The tumour weighed 138 g. and measured 8 by 7 by 5 cm. Histologically it was similar to those of Cases 1 and 6.

Of interest in this case were the attacks of coma with spontaneous recovery. These are discussed later.

Case 8.—E. H., a man aged 47, a costing clerk, was admitted to Leeds General Infirmary in October, 1952, under Mr. W. R. Henderson.

He was complaining of impaired memory for about a year, a left field defect for five months, and mild headache for three or four months.

Fifteen months previously he had had while at work an attack of unconsciousness without convulsion, preceded by a feeling of nausea. When he fell he injured the back of his head and had occipital headache for a few days but was then able to resume work. Since this episode he had often seen his doctor because of insomnia, produced, he thought, by worrying about his work, at which he had become less efficient because of impaired memory.

He had first noticed the left field defect five months previously and he thought it had not become worse during this period.

Headache, which was never severe, had been present for three or four months. It was sub-occipital and above and behind the eyes, not more on one side than the other, usually occurred when wakening in the mornings, gradually disappearing after being up for an hour or so. It had not become more frequent or more severe, appeared only about twice a week, was never associated with vomiting, and never kept him away from work.

He had had no sensory or motor disturbances in limbs or trunk, no facial paraesthesiae and no fits. He was right handed.

On examination the abnormal signs were blurring of the nasal margins of both optic discs with distension of the retinal veins and a left homonymous field defect, absolute to a small object in the lower quadrants but only relative in the upper quadrants. There were no motor, reflex, or sensory changes in limbs or trunk and straight radiographs of the skull were normal.

Lumbar C.S.F. (examined elsewhere) and cisternal C.S.F. were of normal composition.

Cisternal encephalography produced only poor filling of the lateral and third ventricles which were displaced to the left. The larger anterior horn was on the right side and the temporal horns did not fill.

A right carotid arteriogram was then done, but unfortunately only poor films were produced showing displacement of the anterior cerebral artery to the left and splaying of the terminal branches of the middle cerebral artery.

Biopsy, through a burr-hole in the parietal region, showed the tumour to be a meningioma, although this was not suspected at the time because the tumour was very soft and easily aspirated. This operation produced slight impairment of postural sense in the left limbs but no weakness and no increased field defect.

The right carotid arteriogram was then repeated and the antero-posterior and lateral films showed an enlarged anterior choroidal artery ending postero-laterally in a small tuft of vessels (Fig. 7). In addition the lateral films

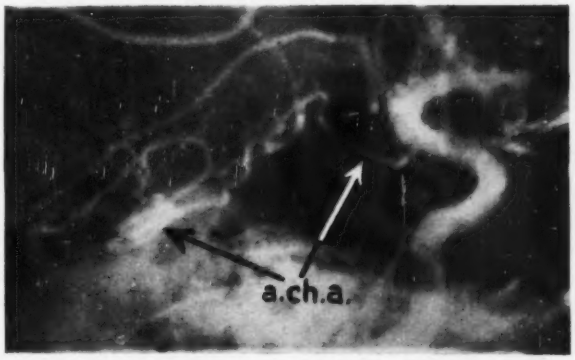

FIG. 7.—Case 8 : Carotid arteriogram showing the enlarged anterior choroidal artery (a.ch.a.) ending posteriorly in a tangle of small vessels.

showed a few small abnormal tumour vessels over an area about 3 cm. in diameter in the region of the trigone.

Vertebral arteriography demonstrated numerous posterior choroidal vessels ascending from the posterior cerebral artery, but no definite outline of the tumour. The normal pattern of the choroid plexus was not seen.

This procedure was followed by craniotomy at which a triangular area of temporo-occipital cortex was excised and the smooth, reddish tumour exposed at a depth of 2 cm. The forward extent of the cortical excision was limited by a large superficial vein. When sufficient of the tumour surface was exposed, its centre was removed by diathermy loop and suction, a procedure which produced profuse bleeding. After the choroid plexus had been divided in the posterior part of the temporal horn and again in the body of the ventricle, the remaining shell of tumour was delivered. Choroid plexus was attached to its surface.

The operation produced no hemiparesis, but joint position sense was, for a few days, lost in the left fingers and toes and the homonymous hemianopia became complete with macular sparing. Postural sense gradually improved and two weeks later was only just detectable. The field defect remained complete.

The remaining shell of tumour measured about 5 by 3 by 2 cm., and with the pieces removed by diathermy weighed 42 g. This was probably about half the weight of the whole tumour, the rest having been sucked away. On the medial aspect of the most anterior part of the tumour in the body of the ventricle was a small nubbin about 0·5 cm. in diameter, which may have been a prolongation through the foramen of Monro. It was impossible to be certain of this at operation because of excessive bleeding.

Histologically the tumour was composed of bundles and whorls of spindle-shaped cells with numerous islands of meningothelial cells and psammoma bodies.

This case was similar to Case 1, in that the only focal sign before operation was the field defect.

Discussion

Diagnosis.—Of the purely clinical diagnosis of these tumours there is little to add to what has already been written by Cushing and Eisenhardt (1938). In their summary they say :

> " One may venture to ascribe a fairly characteristic syndrome to these lateral tumours of the velum, viz. : (1) pressure symptoms with headache tending to be ipsilateral ; (2) a contralateral homonymous hemianopia often bisecting the macula ; (3) a contralateral sensorimotor hemiparesis more marked in the sensory sphere, associated in a few cases with trigeminal numbness ; (4) symptoms suggesting cerebellar involvement in more than half of the cases ; and (5) almost invariably paralexia increased by operation when the tumour, as it commonly does, occupies the left hemisphere."

Unfortunately analysis of clinical material and attempts at formulating a syndrome characteristic of these tumours are not of great help in diagnosis, because their signs are the same as those produced by other tumours occupying the posterior part of the cerebral hemisphere. Many gliomas in this situation will fulfil Cushing's conditions (1), (2), (3), and (5). With regard to (4), consideration of all available evidence shows that signs suggesting a cerebellar lesion are present in only about one quarter of the cases and that these signs appear on the same side as the motor and sensory defects. It must be difficult in the presence of weakness and loss of postural sense to attribute ataxia to cerebellar dysfunction. Although it is probable, therefore, that these tumours cannot be diagnosed by clinical examination alone, they should be considered as possibilities when the syndrome outlined above presents itself.

Plain radiographs of the skull, electroencephalography, and analysis of the cerebrospinal fluid are as a rule of little diagnostic help. Occasionally, as in Case 5, the tumour is sufficiently densely calcified to show on radiographs, but such calcification need not necessarily indicate the pathological type of tumour or its intraventricular position. Usually the most that these radiographs show is evidence of increased intracranial pressure and lateral displacement of the pineal gland.

The E.E.G., which was done in seven cases of the present series, recorded slow waves from overlying brain in all cases except Case 6, where the only asymmetry was of the alpha rhythm. In only one instance however (Case 2) was it of real aid. In this case it provided the first definite indication of the supratentorial position of the tumour, localization of which was not possible from clinical signs alone.

Estimation of protein in lumbar or ventricular C.S.F. is likewise of little help. Of the two the latter is more useful, as it sometimes shows a high protein content of the fluid on the side of the tumour, contrasting with a normal amount from the opposite ventricle, e.g., Cases 2 and 6. This information, however, is not usually available until the ventriculograms have been seen.

In most of the cases previously recorded and in five out of six of the present series in which it was done, ventriculography has demonstrated the intraventricular position of the tumour and also its size. On only one occasion was it of no value (Case 1), no air passing into the affected ventricle from the opposite side. Usually the outline of the tumour is demarcated by air lying anterior to it in the body and temporal horn and posterior to it in the occipital horn. The temporal horn is dilated because of C.S.F. obstruction (Fig. 6) and frequently the occipital horn also is enlarged. The smaller anterior horn is sometimes on the same side as the

tumour, for example, Cases 3 and 5, sometimes on the opposite side, for example, Cases 4 and 6. There is usually considerable displacement of the lateral and third ventricles to the opposite side.

On the whole, therefore, ventriculography provides adequate information before craniotomy is undertaken. In recent years, however, carotid arteriography has often been preferred in investigating cases of suspected cerebral hemisphere tumour. In the present series carotid arteriography demonstrated many features of little specific diagnostic value, for example, displacement of the anterior cerebral artery to the opposite side and elevation and splaying of middle cerebral vessels, features which would be shown by any deep parietal mass. One abnormality, however, which may be characteristic of these tumours was shown in four cases (Cases 1, 5, 7, and 8), namely, an enlarged anterior choroidal artery, ending posteriorly in a small tuft or tangle of vessels near where the antero-inferior extremity of the tumour lay in the temporal horn (Fig. 7). In the other case (No. 6) in which this investigation was done, the poor quality of the films did not permit adequate visualization of the anterior choroidal artery. Only once, in Case 8, were vessels seen within the tumour.

Vertebral arteriography, which was done in four cases, showed in the lateral views one constant feature, namely, absence of the normal pattern of the choroid plexus. Even the opposite plexus was not seen, presumably because most of the contrast medium was taken up by vessels entering the tumour. In addition, the posterior choroidal vessels were abnormally numerous (Cases 5, 6, and 8), or stretched (Case 7). In one instance (Case 5), the tumour was outlined both by encircling vessels and a residual haze. The antero-posterior films, as would be expected, were of little help, because in this view the choroidal arteries are foreshortened.

Visual Fields.—In all except two cases of this series (Cases 2 and 5), there was some field defect before operation, varying from visual inattention to complete homonymous hemianopia. That this is due to a lesion of the optic radiation, especially of its upper fibres passing lateral to the trigone, is suggested by the involvement of the lower rather than the upper quadrants.

In all cases after operation hemianopia was complete and remained so, except in Case 4 in which there was subsequent slight improvement. This increase in the hemianopia following operation is presumably due to damage to the radiation; by an incision through it, by interfering with its blood supply, or by bruising during tumour removal. That this explanation is not the whole story, however, is suggested by Case 2, in which there were full fields before the first (frontal) craniotomy and a complete homonymous hemianopia afterwards.

Facial Paraesthesiae.—In two instances (Cases 4 and 6) sensory attacks in the face on the same side as the tumour were recorded. In Case 4 it was described as a "twitching sensation" not associated with visible movement, and in Case 6 as "tingling". In neither case was there objective sensory impairment.

Effects of C.S.F. Obstruction.—These tumours are so placed that the normal flow of C.S.F. from the temporal horn is impeded and, since they are to some extent movable, it is reasonable to assume that sometimes complete obstruction will occur. Only rarely in the present series did intense paroxysmal headache feature in the history, but in Case 7 there were transient attacks of coma associated with a fixed and dilated pupil, which may have been due to intermittent blockage of the temporal horn.

Gross Features of the Tumours

Site.—Cushing and Eisenhardt (1938), as already mentioned, differentiate between true plexus meningiomas lying wholly within the ventricle and conforming to its shape, and lateral meningiomas of the velum which tend to be globular and lie partly within the ventricle and partly embedded in the cerebral hemisphere. All the tumours in the present series belong to this latter group. It seems probable, however, that such a differentiation is artificial, for whether or not a tumour lies wholly within the ventricle must, to a great degree, depend on its size. As the tumour enlarges the ventricle will distend, but ultimately the ependyma will rupture and the tumour will then be in contact with the white matter.

A good opportunity for studying one of these tumours *in situ* was afforded by the specimen shown in Fig. 8. Little is known of the history of this woman aged 68, who died suddenly at home, except that for two years she had had fits and dizziness and impaired vision in the left eye (possibly a left homonymous defect). The tumour, which weighed 42 g. and measured 5 by 4 by 3 cm., occupied the trigone of the right lateral ventricle and extended backwards into occipital white matter. Histologically it was composed of bundles of spindle-shaped cells with numerous islands of meningothelial cells. It had two main vascular pedicles, both formed of choroid plexus, one passing forwards and downwards into the temporal horn and one medially towards the junction of the body and the trigone.

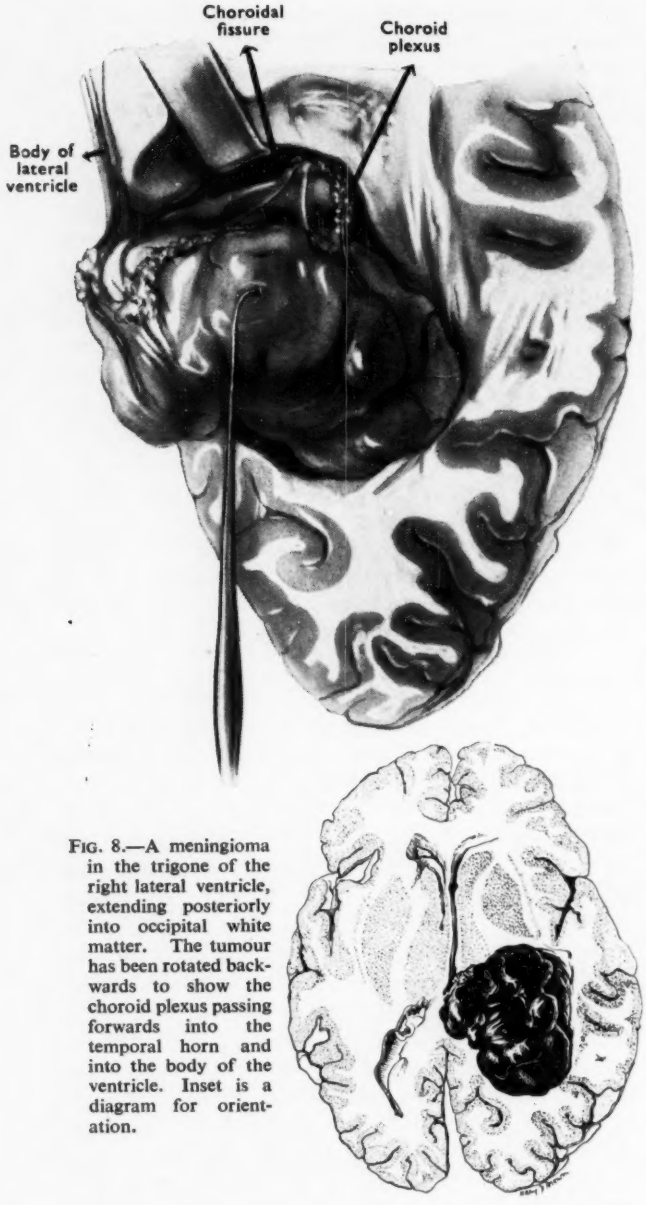

FIG. 8.—A meningioma in the trigone of the right lateral ventricle, extending posteriorly into occipital white matter. The tumour has been rotated backwards to show the choroid plexus passing forwards into the temporal horn and into the body of the ventricle. Inset is a diagram for orientation.

In this latter pedicle, which continued along the body of the ventricle towards Monro's foramen, a large choroidal vein was conspicuous. Between the attachments of the pedicles, choroid plexus was firmly adherent to the tumour but did not encircle it. The tumour was freely movable except for its attachment to the plexus and to a few small veins running from its postero-lateral surface directly into the brain. The occipital lobe white matter into which the tumour had burrowed showed, on histological examination, a gliosed surface layer but no ependyma.

Although belonging apparently to the group of " lateral tumours of the velum ", it is reasonable to suppose that this tumour, at an earlier stage of development, lay wholly within the ventricle and then extended backwards to embed itself in brain.

Blood Supply.—The normal choroid plexus obtains most of its blood from the posterior choroidal arteries ascending into the velum from the posterior cerebral artery. The terminal branch of the anterior choroidal artery entering the plexus is very small, (Alexander, 1942), and, whereas it is single, the posterior choroidal vessels form a group.

Meningiomas arising from the plexus (or velum), in a similar manner to meningiomas elsewhere, produce enlargement of feeding vessels and this is shown in arteriograms as enlarged anterior choroidal arteries or as undue vascularity in the territory of the posterior choroidal vessels.

Microscopic Features of the Tumours.—Abbott and Courville (1942) pointed out that the 50 or so intraventricular meningiomas recorded up to 1942 had, with only one possible exception, been described as fibrous, fibroblastic, or psammomatous. From this and other observations they deduced that there are two main histological types of meningioma : a fibroblastic type, which they suggest originates in the fibrous stroma of the arachnoid, and a meningothelial or syncytial type arising from the " covering " or " cap " cells which form the outer layer of the arachnoid. The present series of cases shows, however, that meningiomas within the lateral ventricle differ from each other in histological structure as do meningiomas elsewhere. Sometimes fibrous cells predominate (e.g., Case 5), sometimes meningothelial cells (e.g., Case 3), but usually both types are seen in varying proportions.

Methods and Results of Treatment.—The treatment of these meningiomas must consist of their removal by operation. There is no reason to suppose that any type of decompression would be useful and radiotherapy would be ineffective in overcoming the obstruction of the temporal horn.

It is, as a rule, technically easy to remove these tumours completely, because their blood vessels are concentrated in two main pedicles and separation from white matter or ependyma is straightforward. They are easier tumours to remove than, for example, many parasagittal meningiomas.

Why then do the results of operation often compare unfavourably with those of meningiomas elsewhere ? One reason, no doubt, is that the surgeon is confronted not only by the unexpected

but also, because of their rarity, by something with which he is unfamiliar. The main reasons, however, are that these tumours are more common on the left side and incision of the overlying brain causes dysphasia.

In most of the published cases and in all of the present series, the tumours were approached by the most direct route. Incisions were made in various parts of the parietal or posterior temporal lobes and deepened until the surface of the tumour was exposed. The separation of the tumour and coagulation of its feeding vessels, as a rule, presented no difficulty.

The usual immediate effects of operation are hemiplegia, gross impairment of discriminative sensations, complete homonymous hemianopia and, if the tumour is in the dominant hemisphere, severe speech disturbance. The hemiplegia rapidly recovers, the sensory loss more slowly and sometimes incompletely, and the hemianopia remains permanently. The ultimate defect, therefore, with a right-sided tumour is a left homonymous hemianopia and perhaps some postural sense loss as in Cases 4, 7, and 8. In all these cases the residual disability was minimal and the patients had resumed their previous employment. The most successful of this group was the patient described as Case 8, in whom the forward extent of the cortical excision was limited by a large superficial vein, a circumstance which although making the operation more difficult no doubt contributed to his rapid neurological recovery. When the approach is through the parietal area a field defect is inevitable, but from Cases 4, 7, and 8 it appears that to cause the least disturbance of discriminative sensation, the cortical incision should be made as far posteriorly and as low as possible.

Following the removal of left-sided tumours, however, there is the added disability of speech and reading, a defect accentuated by the rarity of dysphasia before operation. In all five cases (Cases 1, 2, 3, 5, and 6) some dysphasia will probable be permanent, and in two (Cases 5 and 6) difficulty in reading amounting to almost complete alexia occurred. Despite these defects the labourer (Case 1) and the joiner (Case 2) had resumed their employment and the housewives (Cases 3, 5, and 6) were managing fairly well. Some degree of dysphasia and dyslexia when approaching the tumour through the left posterior parietal region is probably unavoidable but the disability is lessened by planning the cortical incision on the exposed brain as far back as possible and with the least interference to blood vessels.

In this series of eight, fits occurred in four cases, beginning after operation at intervals varying from a few days to five months. In all cases, however, the fits were reasonably well controlled with medication.

Summary

The available literature on meningiomas arising in the lateral ventricle from the choroid plexus or velum has been reviewed. About 50 of these tumours had previously been described.

Eight additional cases have been described and also a specimen showing one of these tumours *in situ*.

The various diagnostic procedures have been evaluated and certain features of carotid and vertebral arteriograms described.

Operative results have been discussed and measures described to minimize post-operative disability, which is usually severe, especially with the more common left-sided tumours.

I wish to thank the physicians and surgeons for permission to publish details of patients admitted under their care at the National Hospital, Queen Square, and the Leeds General Infirmary. Especially I am indebted to Mr. Harvey Jackson and Mr. W. R. Henderson. I am grateful also to the pathologists, Dr. W. Blackwood and Dr. A. F. J. Maloney, to Professor C. J. Polson, of Leeds University, for the specimen illustrated in Fig. 8, and to the publishers for permission to quote from the book " Meningiomas ".

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ISCHAEMIC SENSORY LOSS IN PATIENTS WITH PERIPHERAL NERVE LESIONS

BY

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During an investigation of patients with painful paraesthesiae due to median nerve compression at the wrist it was found that arresting the circulation to the affected arm by a pneumatic cuff sometimes resulted in intense median paraesthesiae, with pain resembling that of the patients' spontaneous attacks. It was also found in these patients that the inflation of a pneumatic tourniquet round the arm might result in the rapid onset of numbness where none had been present before, and that it would make a mild sensory deficit more clear cut. This abnormally rapid failure of sensation in an area of initial sensory impairment did not prove to be restricted to patients with median nerve lesions at the wrist, but was found also in patients with other peripheral nerve lesions.

The object of the present paper is to describe the effects of sudden circulatory arrest on the sensory loss of patients with peripheral nerve and root lesions affecting the hand, and to compare them with the effects of artificially induced ischaemia in normal subjects. The ischaemic paraesthesiae of patients with median nerve lesions have already been described (Gilliatt and Wilson, 1953), and will not be discussed further.

A number of writers have described the effects of arterial arrest on sensation in the normal arm, and there appears to be agreement on the main sequence of changes. The inflation of a pneumatic cuff above the elbow is followed within a minute or so by ischaemic paraesthesiae, the " compression tingling " of Weddell and Sinclair (1947), and this is thought to be due to transient hyper-excitability of the nerve trunks lying under the cuff (Kugelberg, 1944). In normal subjects these ischaemic paraesthesiae usually take the form of a soft, diffuse tingle lasting three or four minutes, felt most strongly on the ulnar side of the hand (Weddell and Sinclair, 1947).

Some 10 to 15 minutes after the beginning of ischaemia the earliest indication of sensory loss appears in the form of a change in the quality of sensation in the finger-tips. When the skin is rubbed it may feel numb and yet rough or prickly, and this change precedes tactile anaesthesia when fine hairs are used for testing (Lewis, Pickering, and Rothschild, 1931 ; Sinclair, 1948). The time of onset of these changes and the order in which the finger-tips become involved is obviously of great importance in relation to the findings in peripheral nerve lesions, and for this reason a fresh series of observations on control subjects has been included in the present work.

Material and Methods

Thirty patients were investigated who were considered to be suffering from median nerve compression at the wrist. Twelve of them, who were studied both before and after operation on the median nerve, formed part of the series of 40 patients with acroparaesthesiae, treated by surgical decompression of the median nerve in the carpal tunnel, reported by Kremer, Gilliatt, Golding, and Wilson (1953). The remainder were patients seen and treated after September, 1952, and therefore excluded from the original report. All of the 30 patients had typical nocturnal attacks of pain and tingling, and in some of them pain was present in the arm as high as the shoulder. In this respect no distinction could be made between the idiopathic group of cases, mostly middle-aged women, and the smaller group of cases in which the syndrome followed definite local trauma to the wrist. Nor were the acroparaesthesiae in those with abnormal neurological signs in the hand different from those without, and every gradation of sensory disturbance was seen, from the merest suggestion of a subjective change to gross anaesthesia throughout the median territory. The average age of the 30 patients with median nerve compression was 47, with a preponderance of females over males of four to one.

The remaining patients who were investigated included four with ulnar nerve lesions, one with a radial nerve lesion, two patients with cervical rib syndromes, and two with cervical disc degeneration causing numbness in the hand.

Fifty patients without any neurological disorder affecting the hand were used as control subjects. The

FIG. 1A

FIG. 1B

majority of them were suffering from general medical diseases, and their average age was 48, with a sex ratio of five females to two males.

Nerve ischaemia was induced by a pneumatic cuff inflated to above arterial pressure round the limb, in most cases on the arm just above the elbow. In all occlusions at this level a rubber bag 6 in. by 15 in. was used in a wide sleeve so that the arm was uniformly compressed. Cuff pressures of 200 to 220 mm. Hg were adequate save in hypertensive patients in whom 250 to 260 mm. Hg was required. Even this pressure was well tolerated for short periods.

To induce ischaemia of nerves in the forearm the same pneumatic cuff was suitable, but as the arteries and nerves in this region are partly protected from compression by their relation to bone, pressures of 220 to 260 mm. Hg were required to prevent venous congestion in the hand. A cuff round the forearm gave rise to some discomfort, owing to local compression of muscle, and in a few experiments a narrow cuff round the wrist was used (Fig. 1A). In this position there was little muscle directly under the cuff, but higher pressures were needed for complete arterial occlusion.

For local compression of the digital arteries a cuff 2¼ in. by 4 in. was suitable (Fig. 1B), and by a simple modification of the technique it was possible to produce local ischaemia in all the fingers simultaneously (Fig. 2). In these experiments cuff pressures of 260 to 280 mm. Hg were used, and in fact caused no discomfort. The relative scarcity of muscle in the finger seems to be the factor which permits pressures of this order to be maintained without pain, as is also the case at the wrist.

In most experiments the arm was raised for 15 seconds before the inflation of a cuff, and then lowered and rested comfortably with the palm uppermost, care being taken to avoid local pressure on the ulnar nerve. Except in special cases the simplest possible method of sensory testing was adopted, the examiner merely stroking the tips of the patients' fingers with his own, and this massive stimulus was usually felt to be altered in some way before formal testing revealed any abnormality. However, to confirm the results obtained by this simple test, a graded set of tactile hairs was used, made up from suitably mounted nylon threads to give a range of stimuli from 0·3 g. to 9·0 g. Although nylon imbibes water unless kept in a desiccator, little fluctuation in the bending strain of the hairs was noted from one experiment to another.

In a few experiments the arm was immersed in a water bath at 37°–38° C. to above the elbow, after lightly greasing the finger-tips, as described by Lewis and others (1931). When this was done the fingers could be lifted out and tested when necessary without appreciably cooling the skin. An area of skin on the finger-tip was ringed and tested by a run of five or 10 stimuli in

FIG. 2

succession; the subject was told not to guess, and by irregular spacing of the stimuli random answers were easily detected. As sensation failed during ischaemia, it was possible to lift the greased fingers out of water each minute, and to perform 10 tests within this period. Thus, if two separate areas were being tested, runs of five stimuli were used for each, whereas if only one area was concerned runs of 10 were possible every minute.

Some fatigue in the subject was usually noted in a run of 10 tests, and when the stimuli were near threshold the last few were often missed. This fatigue effect always disappeared by the next minute, and no progressive deterioration from this cause was noted in experiments lasting up to 20 minutes. This was shown by the fact that the tactile threshold would usually return rapidly to normal after release of the circulation, although the subject might by then have been tested 150 or 200 times.

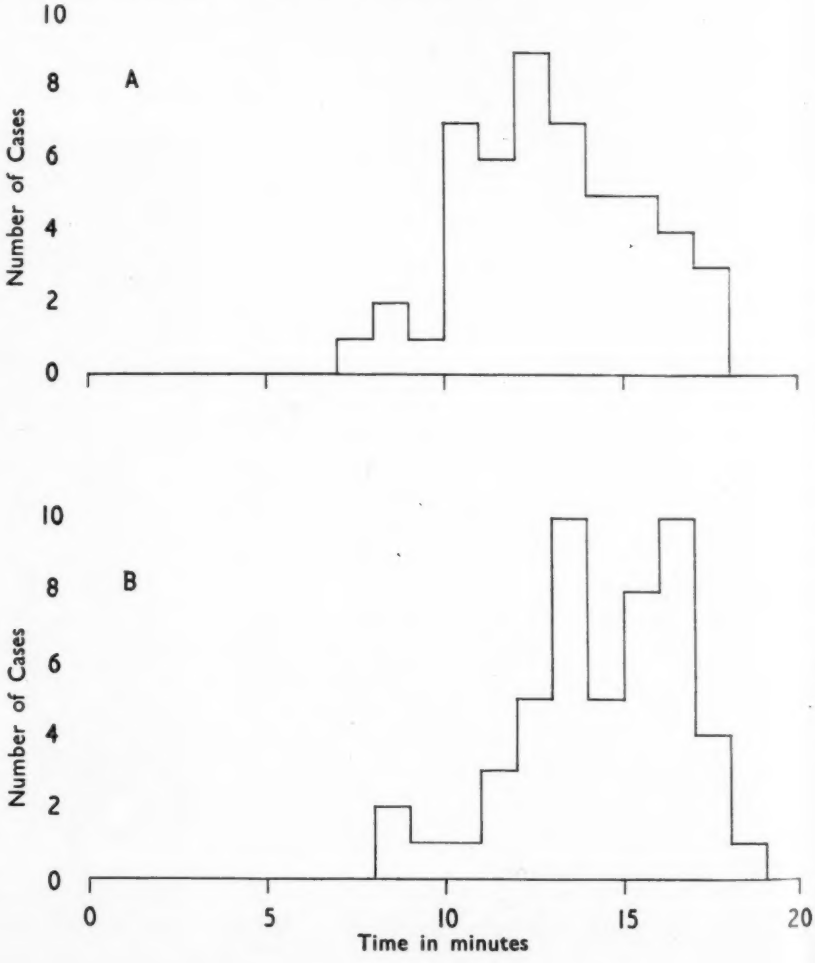
Results

Ischaemic Sensory Loss in Normal Subjects.—Within a few minutes of inflating a cuff round the arm, ischaemic paraesthesiae would be reported by most subjects, but as these subsided sensation appeared to return to normal, and no further change would occur for several minutes. Between 10 and 15 minutes after the onset of ischaemia, however, patients reported a noticeable alteration in the quality of the sensation produced by rubbing the finger-tips, and the time at which this occurred could be elicited quite easily by careful questioning. The hands were occasionally described as "cold" or "numb" much earlier in the experiment, but in these cases enquiry revealed that the skin of the finger-tips was still as sensitive as on the other side, and the later change in the sensation produced by rubbing or stroking the pads of the fingers was immediately recognized by patients when it occurred. The change was described in a variety of ways by different patients; some referred to the feeling as "glassy" or "smoother than normal", while others described it as "rough", "numb but sensitive", and later definitely "prickly". It was commonly recognized that the finger had "gone to sleep" and was "dead" or "numb", as if it had "been in the snow".

Weddell and Sinclair (1947) referred to this change as "velvety numbness" and considered that it was similar to the sensation of rubbing velvet between the fingers, but when this analogy has been suggested to patients they have usually rejected it and preferred some less picturesque description, such as one of the terms mentioned above.

In all the patients, the appearance of subjective numbness of the skin when it was rubbed or stroked proved a most reliable indication of early sensory failure. If there were any doubt as to its presence, it was often useful to ask the patient to confirm the change by feeling the affected finger-tips with his other hand, and when sensation was examined in

FIG. 3.—Time to onset of ischaemic numbness, pneumatic tourniquet placed above the elbow. A: time to onset of numbness in one finger in 50 control subjects. B: time to onset of numbness in all fingers in control subjects.



this way the results were as consistent as those obtained by careful tests with graded nylon threads. In the majority of patients, stroking of the finger pads was the only method of testing employed, and the term " subjective numbness " has been adopted to indicate sensory loss detected in this way.

Subjective numbness often occurred first in the thumb and spread gradually from finger to finger across the hand, affecting the little finger a minute or two later. Although this spread from radial to ulnar border was not invariable, it was common and occurred in 23 of the 50 control subjects. In seven of them subjective numbness was present in the tips of the fingers supplied by the median nerve for a minute or more before the other fingers were affected.

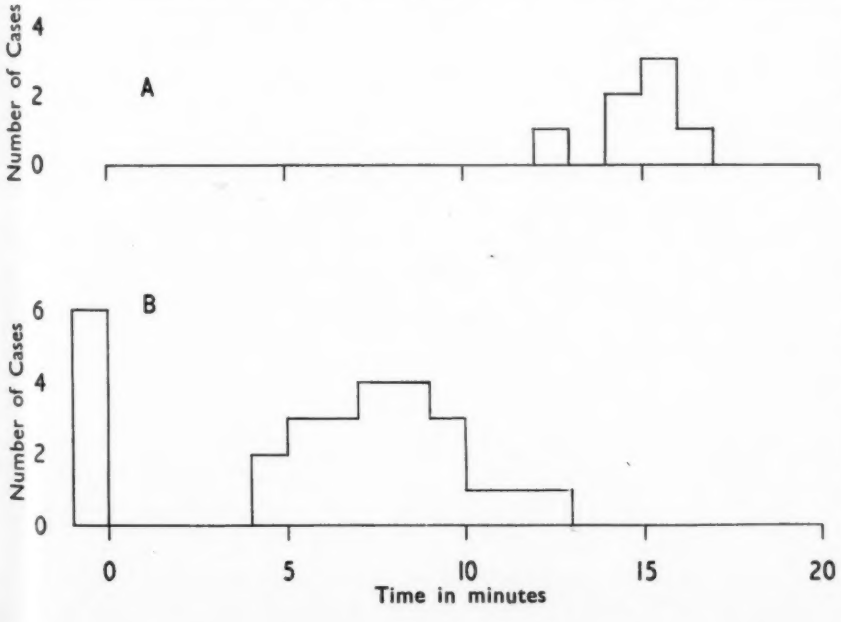
It was uncommon for numbness to appear first in the fifth finger, and in only one of the 50 subjects did ulnar sensory loss involving one-and-a-half fingers clearly precede any change in the rest of the hand. The patient concerned had been bedridden for many weeks, and although no other signs of ulnar nerve damage were present the possibility of a decubitus ulnar nerve lesion was considered.

The reason for the unequal involvement of different fingers in the normal hand is obscure. Sinclair (1948) considered that individual peripheral nerves were normally affected in a definite sequence during ischaemia, and that a difference between median and ulnar territories could usually be demonstrated in the normal hand at some stage of sensory failure. In our own cases clear-cut differences between the median and ulnar fingers were uncommon, and this appeared to be due to the fact that ischaemia was not usually continued beyond a very early stage of sensory failure. If the experiment were continued beyond this point, it often happened that sensory loss, which had appeared almost simultaneously in all the fingers, would gradually become more marked in the median than the ulnar territory, the difference becoming increasingly obvious as the anaesthesia increased.

The earliest time at which subjective numbness appeared in any digit was recorded in each case, and when, after a further interval, numbness was clearly present in all the finger-tips, the time was again noted. The results in 50 control subjects are shown graphically in Figs. 3A and 3B. From these it can be seen that the " time to numbness " for the earliest digit to be affected varied from 7 minutes to 17 minutes in different subjects with a mean of 12·5 minutes (S.D. ± 2·4). The time required for the numbness to involve the tips of all digits was slightly longer, ranging from 8 minutes to 18 minutes (mean 14·0 minutes, S.D. ± 2·3). In all the cases recorded in this way, the site of arterial occlusion was above the elbow.

In the seven control subjects in whom the median territory appeared to be involved one minute or more before any change occurred in the ulnar fingers, the " time to numbness " for the median-supplied digits is shown in Fig. 4A. From this figure it can be seen that in no case was the median numbness present within 10 minutes of the onset of ischaemia.

FIG. 4.—Time to onset of ischaemic numbness, pneumatic tourniquet placed above the elbow. A : time to onset of median numbness in control subjects. B : time to onset of median numbness in carpal tunnel syndrome.
(Median numbness was already present initially in six cases.)



In the experiments in which careful sensory tests with nylon threads were carried out, the findings were of great interest. An early deterioration in performance occurred associated with ischaemic tingling, but, as the latter subsided, awareness of the stimuli improved and did not fall off again until a well marked subjective change was present (Fig. 5). This was the case even when the stimulus was so close to the tactile threshold that a

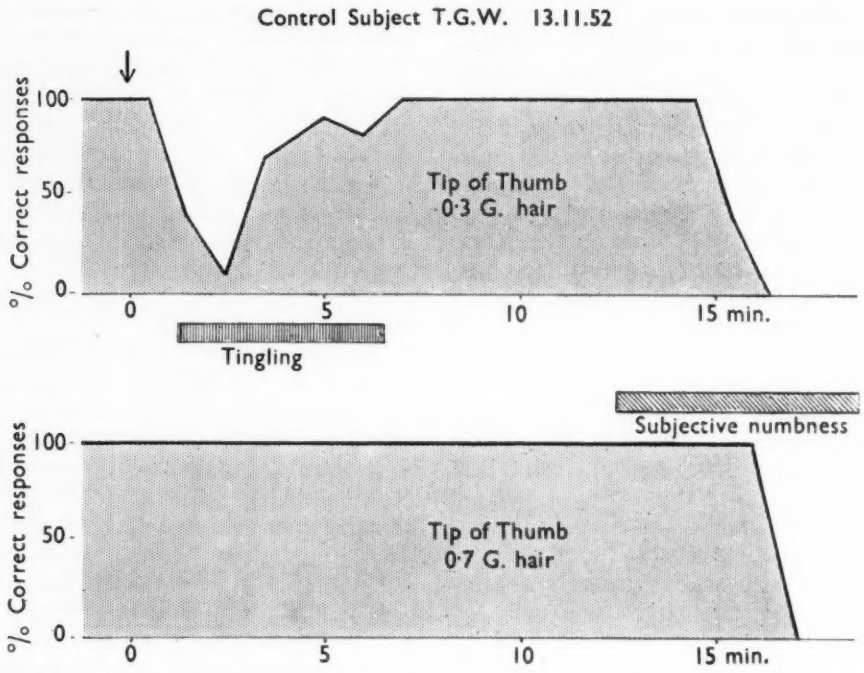


FIG. 5.—Control subject, left arm in water bath at 37° C. Ten tests per minute, tip of thumb; ischaemia at arrow, from pneumatic tourniquet above elbow.

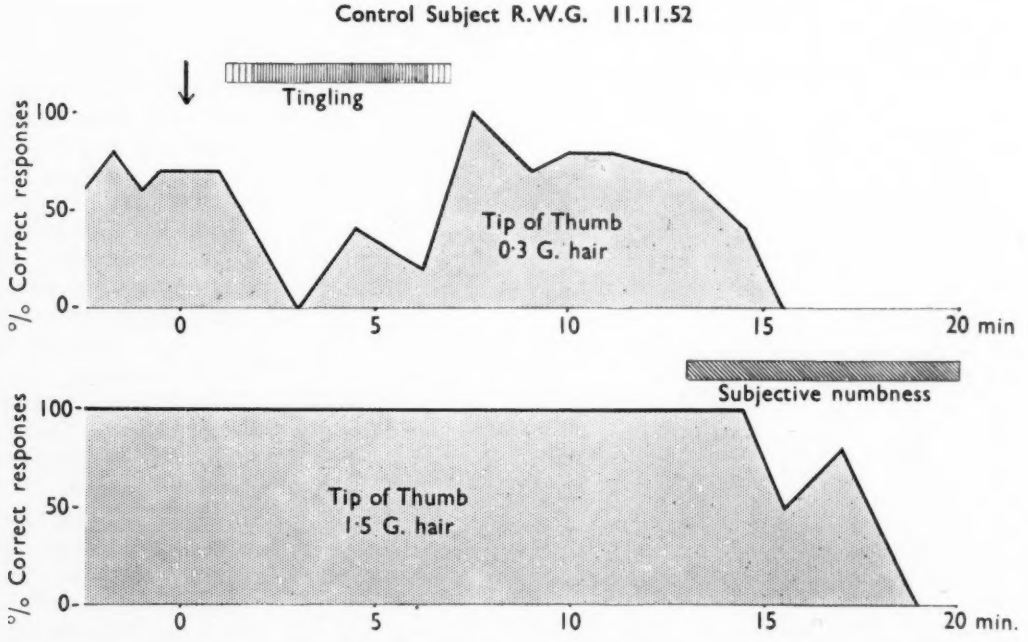


FIG. 6.—Control subject, left arm in water bath at 37° C. Ten tests per minute, tip of thumb; ischaemia at arrow, from pneumatic tourniquet above elbow.

proportion of touches was being missed before the ischaemia had begun (Fig. 6). After release of the circulation, sensation usually returned to normal within 30 seconds, but a second rise in tactile threshold always occurred as soon as post-ischaemic pricking and tingling began.

Ischaemic Sensory Loss in the Carpal Tunnel Syndrome.—Thirty patients with median nerve compression at the wrist were subjected to a period of ischaemia long enough to produce numbness of the fingers. In 20 patients some subjective numbness was already present in the hand, but in only six did it involve the whole median distribution. In all cases existing sensory loss became very much more obvious during ischaemia and in the 14 patients with partial median nerve involvement, numbness spread within a few minutes to the remaining fingers supplied by the nerve, the ulnar territory remaining normal.

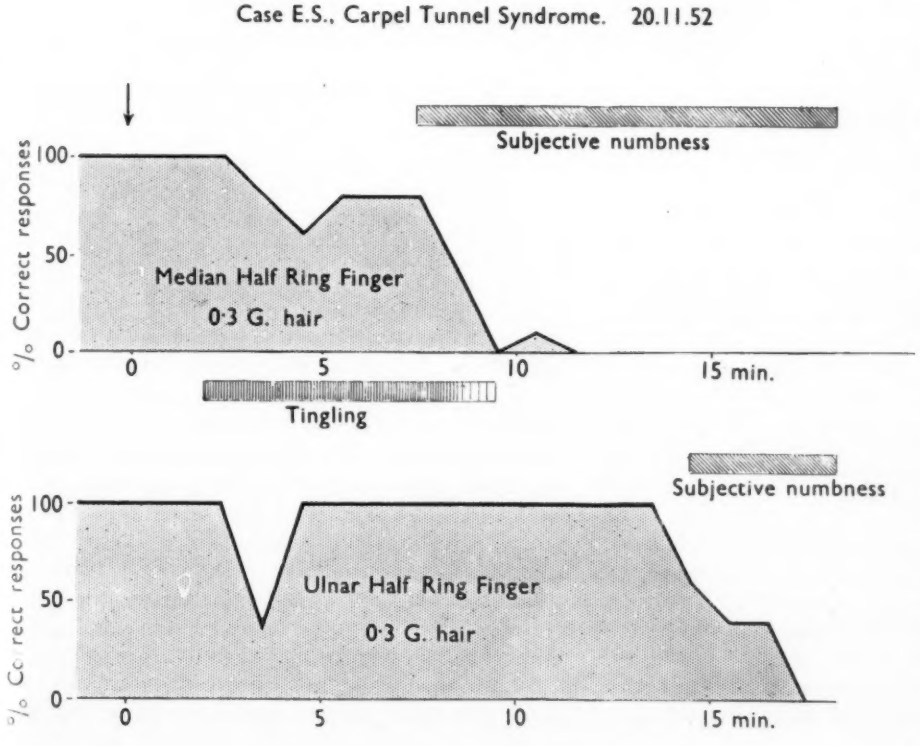
In the 10 patients without subjective numbness of the hands, ischaemia caused it to appear in a median distribution in seven, with a well-marked difference between the two sides of the ring finger. In only three of the 30 patients did a median distribution of numbness fail to occur at all during ischaemia. Two of the three failures were in mild early cases for whom operation had not been advised, and in the third the test was negative at first, but subsequently became positive while the patient was awaiting admission to hospital.

The earliest time by which subjective numbness was present in all the median-supplied digits was noted in each case and is shown graphically in Fig. 4B. From this it can be seen that in the 28 cases in which it occurred, the " time to numbness " for the median fingers ranged from zero to 12 minutes, and that in 26 cases the numbness was present within 10 minutes.

The early onset of median sensory loss during ischaemia was easily confirmed by quantitative tests with graded hairs, and one experiment is illustrated in Fig. 7. In this patient slight subjective sensory loss was present initially in the thumb, index, and middle fingers, but the ring finger was described as normal. During ischaemia subjective numbness developed on the median side of the ring finger after eight minutes, with anaesthesia to the 0·3 g. hair by 10 minutes, the corresponding changes on the opposite side of the finger occurring after a further seven or eight minutes of ischaemia.

In that it often provided confirmatory evidence of median nerve damage, the inflation of a pneumatic tourniquet round the arm was of considerable practical value in obscure cases of acroparaesthesiae, as is shown by the foliowing cases.

FIG. 7.—Carpal tunnel syndrome, left arm in water bath at 37° C. Five tests per minute on each side of ring finger ; ischaemia at arrow as in Fig. 5.



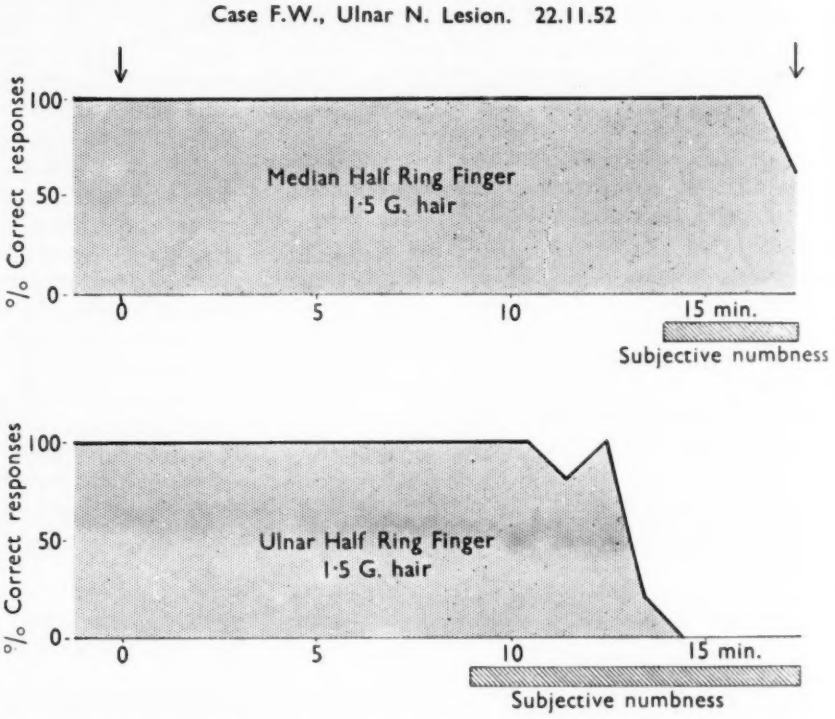
Mrs. E. W.—This patient aged 55 had attacks of painful tingling in both hands at night, the right more than the left, with numbness of the fingers on waking, for many years. Examination of the right hand revealed subjective numbness of the middle finger, with a slight change in the index and median half of the ring finger, but sensation in the thumb was described as normal. The right arm was placed in water at 37° - 39° C. and a pneumatic cuff inflated

to 220 mm. Hg above the elbow. Ischaemic tingling was not abnormal, being mild in intensity and most marked in the ulnar fingers, but when, after five minutes, the hand was withdrawn from the water-bath and dried, the median fingers and thumb were definitely numb, particularly at the tips, and the patient described them as " much more dead " than before the experiment. The hand was replaced in water and when it was taken out and retested after 10 minutes, the thumb, index, and middle fingers, and half the ring finger were described as " very dead ", the ulnar fingers being normal. The hand was replaced in water and the tourniquet released, resulting in generalized post-ischaemic paraesthesiae, and a rapid return of sensation to its initial condition.

Mrs. N. G.—This patient aged 53 had had nocturnal attacks of pain in both arms for many years, with tingling in the fingers and aching in the arms as high as the shoulder. Examination revealed subjective numbness of the index and middle fingers with an unpleasant prickly component when they were touched, and slight numbness of the thumb, but the median half of the ring finger was described as " more sensitive " than the ulnar half. Testing with a pin gave inconclusive results owing to horny skin, but suggested if anything an ulnar distribution of hypalgesia. Careful testing with compass points showed some diminution in sensation on the median fingers. A pneumatic tourniquet was inflated round the arm and resulted in tingling that was normal in intensity and distribution, but by five minutes the thumb, index and middle fingers were " dead " and the median half of the ring finger prickled when touched. By nine minutes these fingers were " very dead " and it was possible to demonstrate a change described as " numbness and a buzz " all over the median territory in the palm, the ulnar fingers and hypothenar region and the back of the hand and proximal phalanges remaining normal until 12 minutes when the cuff was released.

Ischaemic Sensory Loss in Other Nerve Lesions Affecting the Hand.—Four patients were seen with mild ulnar nerve lesions due to pressure at the elbow. In all four patients there was slight sensory impairment initially in the fifth finger, but in only two of them was there a difference between the two sides of the ring finger. Early ischaemic sensory loss occurred in all four cases, one of them being illustrated in Fig. 8. Within 10 minutes of the onset of ischaemia well marked numbness of the fifth finger and of half the ring finger was present in each case,

FIG. 8.—Ulnar nerve lesion at the elbow, left arm in water bath at 37° C. Five tests per minute on each side of ring finger ; ischaemia at arrow as in Fig. 5.
Heavier hair was used for testing than in previous figures.



and was obvious to the patient when he touched the area with his other hand. During the next 10 minutes, however, two of the patients showed a gradual reversal of the pattern of sensory loss, the normal progression of sensory failure over the median-supplied digits " overtaking " that of the ulnar fingers, so that at the end of 20 minutes anaesthesia was most dense over the thumb and radial border of the hand. This phenomenon is further discussed in a subsequent section.

Until this time it had been assumed that the effect of ischaemia was a direct one on the damaged nerve fibres at the level of the lesion, but in two of the patients with ulnar nerve lesions, cuffs were inflated round the forearm and the results were found to be similar to the effects of arterial occlusion above the elbow. Subsequently one patient was seen with a mild radial nerve lesion, whose history left no doubt that the site of the lesion was in the musculospiral groove. Slight sensory impairment was

present over the dorsal surface of the first interdigital cleft and proximal phalanx of the thumb, and in this patient also rapidly worsening sensation over the affected area resulted from circulatory arrest in the forearm.

Two patients were then studied with slight subjective sensory loss of a C7 root distribution due to cervical disc degeneration. In both of them the sensory loss was of long standing and had shown little change in the six months before testing. The effects of ischaemia followed the pattern already described, a change in the area of initial sensory loss preceding the onset of numbness elsewhere in the hand.

In these patients, whose nerve lesions were proximal to the pneumatic cuff, it seemed likely that the effect of ischaemia depended upon the additive effect of two quite separate regions of depressed function along the nerve, one at the site of the initial lesion, and the other in the peripheral segment of nerve artificially deprived of its blood supply. Some confirmation for this theory was provided by the following experiment.

Dr. P. B.—This patient, aged 29, in July, 1950, sustained a deep laceration of the palm of the right hand with complete severance of the palmar branch of the median nerve supplying the contiguous surfaces of the index and middle fingers. Primary suture was carried out within an hour of injury, and partial recovery of sensation occurred within six months, but no further change had been noticed since. At the time of examination in November, 1952, there was slight subjective numbness of the contiguous surfaces of the index and middle fingers, with a raised tactile threshold to hairs. Ischaemia was induced by the inflation of four small pneumatic cuffs round the fingers, as in Fig. 2. No change in sensation was detected after 10 minutes, but by 20 minutes marked deterioration had occurred in the hypaesthetic areas, no demonstrable alteration in the responses to graded hairs resulting elsewhere in the hand until 30 to 40 minutes. The difference between the normal and abnormal areas was particularly well brought out by the very gradual loss of sensation which is characteristic of local ischaemia of the fingers.

Further Experimental Observations in Normal Subjects.—In the patients described in the preceding section, ischaemic sensory loss had appeared earlier in a region where sensation was already impaired than elsewhere, irrespective of the site of the lesion relative to the cuff, and it seemed likely that the phenomenon depended upon simple summation of the effects of two separate nerve blocks at different levels. An alternative hypothesis remained that the nerve fibres distal to an injured segment might have undergone some mild degenerative change rendering them more susceptible to ischaemia. In order to decide between these two possibilities the following experiments were carried out.

In a normal subject local ischaemia of the ring finger was produced by a cuff round its base. Simultaneously an ulnar nerve block was produced above the elbow by suspending the arm from a broad strap passing round the limb just above the medial condyle of the humerus, as described by Zotterman (1933). When this was done there was a brief period in which slight subjective numbness was present over the fifth finger due to the strap, and over the median side of the ring finger due to the cuff, with more marked numbness of the ulnar side of the ring finger due to summation of the two, and it was possible to select a hair which was felt on the former two areas and missed altogether on the latter. Technically this was not a very easy experiment to carry out, as the two nerve blocks developed at different rates, but it was repeated successfully on more than one occasion, and the effect reversed by releasing either the strap or the cuff at the critical moment.

In a second similar experiment, a cuff was inflated round the ring finger and shortly afterwards a partial ulnar nerve block was produced by injecting procaine into the ulnar nerve at the elbow. The resulting anaesthesia was mild over the fifth finger, as was the sensory loss over the median-supplied half of the ring finger due to the cuff, but over the ulnar half of the ring finger there was marked sensory loss, with complete anaesthesia to a 0·7 g. hair, which could still be felt without difficulty over the rest of the hand. Release of the finger cuff then resulted in prompt improvement, sensation on the ulnar side of the ring finger improving until it approximated to that over the remainder of the ulnar territory.

From these results it may be concluded that two separate regions of depressed function along a nerve have an additive effect in causing sensory loss in excess of that produced by either block alone.

"Time to Numbness" as a Test of Sensory Recovery.—Two patients with cervical rib syndromes were studied. Both showed mild weakness of the intrinsic muscles of the hand, with a slightly raised tactile threshold to hairs, particularly along the ulnar border of the hand and forearm. In neither case was there any evidence of arterial insufficiency or vasomotor disturbance in the arm itself, and the radial pulse was not easily obliterated by the usual manoeuvres.

Both these patients were tested repeatedly with ischaemia before and after operation, and the results

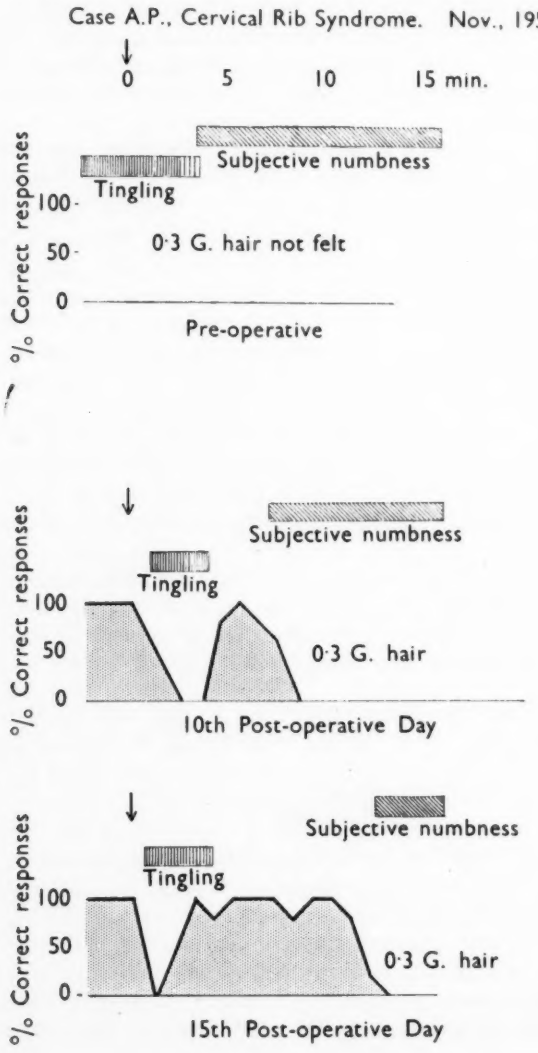
in one of them are shown in Fig. 9. In this patient spontaneous tingling was present continuously in the fingers before operation, and the 0·3 and 0·7 g. hairs were not felt. When a pneumatic cuff was inflated above the elbow, tingling in the fingers increased for a few minutes and then declined, and within four minutes the patient complained that the fingers were " numb " and " dead ".

Ten days after resection of the cervical rib the hand was apparently normal, all tingling having disappeared, and the 0·3 g. hair was easily felt on all fingers. At this time no errors occurred in discrimination of the two points of a compass 0·5 cm. apart. However, a pneumatic tourniquet round the arm produced subjective numbness within seven minutes, and it was on the fifth finger that responses first failed to the touch of a hair.

A further test on the fifteenth post-operative day gave a much more normal result, sensory loss appearing first on the radial side of the hand and involving the fifth finger after 12 minutes.

This result shows that for a single patient repeated measurement of the " time to numbness " can give a reliable quantitative estimate of sensory recovery. It also indicates that the " time to numbness " may still be abnormal at a stage of recovery when formal tests of superficial sensation reveal no abnormality.

FIG. 9.—Cervical rib syndrome, left arm at room temperature. Five tests per minute, tip of fifth finger : ischaemia at arrow as in Fig. 5.



Discussion

In patients with severe compression of the median nerve at the wrist, arrest of the circulation to the arm has been shown to result in intense paraesthesiae and pain, followed by rapid sensory failure throughout the median territory (Gilliatt and Wilson, 1953). At first it seemed likely that these changes were due to a direct effect of ischaemia on the damaged segment of the nerve in the carpal tunnel, but later studies of other peripheral nerve lesions somewhat modified this view, as it appeared that any area of sensory impairment might be adversely affected by ischaemia, regardless of the site of the lesion relative to the occluding cuff.

In their original investigation of the effects of circulatory arrest in normal subjects, Lewis and others (1931) showed that the earliest ischaemic sensory loss was due to depression of function in the segment of nerve immediately underneath a cuff. In one of their experiments slight sensory loss was produced by a cuff round the arm ; a second cuff was then inflated round the forearm and the upper cuff released, as a result of which numbness disappeared from the fingers, although the circulation had not been restored to the distal part of the limb. With longer periods of circulatory arrest, ischaemia of nerves distal to the cuff did contribute to the sensory loss, and local return of the circulation above the elbow did not restore normal sensation to the hand.

At the suggestion of Dr. Michael Kremer the experiment of Lewis and others (1931) was repeated in three patients with severe acroparaesthesiae due to median nerve compression at the wrist. When, after five or six minutes, intensely painful paraesthesiae with numbness of the fingers had been induced by a cuff above the elbow, a second cuff was inflated just above the wrist and the upper one released. In all three patients painful paraesthesiae and numbness persisted and appeared to be unchanged

until the lower cuff was released. Detailed sensory testing was not possible in these patients owing to severe pain in the hand, but the conclusion seemed inevitable that the segment of nerve in the carpal tunnel was in fact more sensitive to deprivation of its blood supply than the proximal part of the nerve above the elbow. The result is thus in contrast to that of Lewis and others (1931), in whose normal subjects the peripheral portions of the nerves contributed little to the early sensory disturbance resulting from a cuff above the elbow.

From this it may be concluded that in patients with peripheral nerve lesions distal to an occluding cuff round the arm, the resulting sensory loss in the hand may depend in part upon a direct effect on damaged nerve, whereas in patients with lesions proximal to an occluding cuff the result must be due to the simple additive effect of two separate regions of depressed function.

In order to relate the severity of nerve damage to the sensory experience, it is obviously essential to know what proportion of afferent fibres must cease to conduct before detectable sensory loss results. Magladery, McDougal, and Stoll (1950) inflated a cuff round the forearm in a normal subject and stimulated the ulnar nerve at the wrist, recording the nerve action potential at the elbow, as described by Dawson and Scott (1949). Their paper provides little information about the sensory loss produced, but their records show a decrease in size of the afferent volley to less than two-thirds of normal within nine minutes of the onset of ischaemia. At this time no sensory change in the fingers would be expected from a cuff round the forearm.

If in fact 30–40% of nerve fibres cease to conduct before detectable sensory loss appears, the effect of ischaemia in our patients with ulnar nerve lesions becomes more intelligible. As a tentative theory it might be suggested that if 25% of the tactile fibres in the ulnar nerve were blocked by a local lesion at the elbow, this deficit might not be detectable clinically. If 25% were also blocked by local ischaemia in the forearm, the total deficit would be 44% (25 + 25% of 75), a proportion which might give rise to easily detectable numbness of the skin. Loss of function in 50% of fibres under the cuff would cause a total deficit of 62·5%, and blockage of 75% under the cuff a total of 81%. By this stage a normal nerve trunk would have lost 75% of its fibres, and as complete anaesthesia was approached the difference between normal and abnormal areas would become less marked. This would explain the observation that in mild ulnar nerve lesions sensory deterioration occurred first in the ulnar fingers during ischaemia, but was later " overtaken " by the normal progress of anaesthesia starting on the radial side of the hand.

In the diagnosis of peripheral nerve lesions, the use of a pneumatic tourniquet to confirm the presence of minimal sensory loss has much to recommend it. In suspected ulnar nerve lesions, the appearance of ischaemic sensory loss restricted to the ulnar fingers is probably valid evidence of a pre-existing lesion of the nerve, as early sensory loss of this distribution does not appear to occur in the normal hand as the result of a cuff above the elbow. In suspected median nerve lesions, however, the results are more difficult to interpret as the median nerve appears to fail first in a proportion of normal subjects, and the rapidity with which sensory loss occurs is therefore of critical importance. Whereas numbness restricted to the median-supplied digits and present within five or six minutes of the onset of ischaemia is clearly abnormal and indicative of a lesion of the nerve, a similar change occurring after a longer period carries less certainty. However, when the results in the patients with median nerve lesions (Fig. 4B) are compared with those in the control group (Fig. 4A), the differences are such that it seems reasonable to accept any well marked median sensory change within the first 10 minutes of ischaemia as suggestive of median nerve damage, particularly if a further interval of several minutes elapses before involvement of the remainder of the hand.

When using ischaemia in the examination of peripheral nerve lesions, it has been possible to test sensation very simply by a massive stimulus such as the examiner's finger, and little advantage has been obtained from using a wisp of cotton wool or graded hairs. This is in accord with the observations of Lewis and others (1931), and of Weddell and Sinclair (1947), who used 0·6 and 0·5 g. hairs respectively, and found that a subjective change in the sensation aroused by a massive stimulus preceded the onset of anaesthesia to the hairs. Zotterman (1933) used a wide range of V. Frey hairs to test sensation during ischaemia, and refers to a " slow creep upwards of the threshold for the hairs from about eight minutes ". Few experimental details are described, and the number of stimuli, skin temperature, and time of onset of subjective numbness are not stated. From the only figures displayed it appears that in one of his subjects a 0·2 g. hair was still felt after 10 minutes, a result incompatible with any considerable rise in threshold. In theory it is possible that an earlier change in tactile threshold does occur during ischaemia, but the technique used in the present work has not been sufficiently sensitive to demonstrate it. From the practical point of view

there is every advantage to be gained from recording merely the subjective sensation in response to a massive stimulus, as this is easily determined in unintelligent patients, and is much less affected by horny skin or cold hands than more elaborate methods of sensory testing.

In control subjects and in patients with peripheral nerve lesions it was found that ischaemic and post-ischaemic tingling were accompanied by a marked deterioration in the perception of fine hairs, and paraesthesiae that were scarcely perceptible to the subject seemed to cause a disproportionate change in the tactile threshold. It is surprising that an increase in the excitability of afferent nerve fibres should result in impairment of sensation, particularly when it is remembered that heavier stimuli actually reinforce post-ischaemic pricking and tingling and may result in marked reflex changes (Gilliatt, 1952). A raised tactile threshold associated with over-reaction to a stimulus that is perceived is analogous to the common clinical combination of hypalgesia and hyperpathia, and suggests that the latter might result from a similar increase in the excitability of pain fibres.

Summary

In 40 patients with peripheral nerve and dorsal root lesions affecting the hand, and in 50 control subjects, the circulation to the arm has been arrested by a pneumatic tourniquet above the elbow. During this period of artificially induced ischaemia, tactile sensation in the fingers has been tested repeatedly in each case in order to ascertain the time at which sensory failure occurs.

In 50 control subjects the average duration of ischaemia required to produce sensory loss in the skin of the fingers has been 14 minutes (S.D. ± 2·3).

In the patients with peripheral nerve lesions, ischaemic sensory loss has occurred with abnormal rapidity within the distribution of the affected nerve, and pre-existing sensory loss has become much more marked, a change usually being apparent within five or 10 minutes of the onset of ischaemia.

In the case of median nerve lesions at the wrist, the early sensory failure caused by circulatory arrest appears to be due in part to an increased susceptibility to ischaemia of damaged nerve fibres at the site of the lesion. However, in patients with peripheral nerve and root lesions proximal to the site of a pneumatic tourniquet, abnormally rapid failure of sensation also occurs during ischaemia, and in these cases the result appears to be due to the additive effect of two separate regions of depressed function along the course of the nerve, one at the site of the lesion and the other under an occluding cuff.

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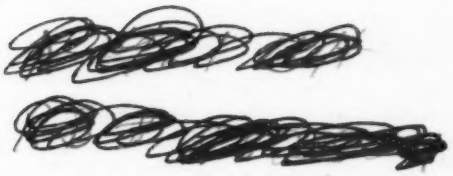

MEMORY DISTURBANCES IN THIRD VENTRICLE TUMOURS

BY

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As has been stated by Busch (1940), the study of localized disease of the brain has always had especial interest because it raises the possibility that analysis of the concomitant psychological disorders may clarify some of the connexions between mind and brain.

A mental function of basic interest and importance is that of memorizing, and considerable efforts have been made to define the lesions involved in impairment of this function. Although it is now widely recognized that some degree of memory is involved in all forms of intellectual behaviour, and, at the same time, some degree of memory impairment always accompanies intellectual deterioration, cases are not infrequently observed in which the ability to retain and recall recent events seems to be impaired out of all proportion to other mental defects. Such cases, first described by Korsakov (1889), can occur in a variety of different clinical conditions, but there is a considerable volume of literature suggesting that the accompanying lesions tend to centre around the floor and sides of the third ventricle. Thus, in the necropsy studies of patients who during their lives had shown Korsakov's psychosis from chronic alcoholism Gamper (1928) found that the majority of lesions were concentrated around this area, while conversely Campbell and Russell (1941) noted that in the clinical history of patients with Wernicke's lesions acute confusional and amnesic states were extremely frequent. Again, Busch (1940) concluded from his analysis of the mental disturbances seen in 662 unselected tumour cases that impaired memory, while not closely associated with raised intracranial pressure, was most frequent in the intracerebral lesions surrounding the third ventricle.

Papers have also appeared from time to time reporting individual cases of amnesic states due to localized lesions which were verified by operation or at necropsy. In these instances the lesion has always been a deep mid-line one, involving the grey matter around the third ventricle (Foerster and Gagel, 1934 ; Lhermitte, Doussinet, and Ajuriaguerra, 1937 ; Hermann, 1950 ; Benedek and Juba, 1941 ; Conrad and Ule, 1951 ; Sprofkin and Sciarra, 1952). In the case reported by Foerster and Gagel, that of a cranio-pharyngeal cyst, the mental symptoms cleared up as soon as the cyst was emptied and the cyst wall surgically removed.

As against these reports, however, there are also a great many other observations indicating that the impairment of memory is a frequent and non-specific sequel to diffuse and widespread brain damage. Carmichael and Stern (1931) examined the brains of five patients said to have exhibited Korsakov's syndrome and noted that the histological changes were chiefly seen in the cortex of the prefrontal areas. In only one case were there additional lesions in the thalamus. Walther-Büel (1951) studied the psychiatric disturbances in 600 unselected tumour cases and found that the " organic psycho-syndrome ", consisting largely of memory impairment, occurred in the vast majority of all those over 40 years old. McFie and Piercy (1952), from a systematic psychological study of patients with localized brain lesions, also concluded that general failure of retention, irrespective of the material to be retained or locus of the lesion, was the most common defect. Finally, specific studies of the mental symptoms associated with colloid cysts of the third ventricle indicate that, although memory disorders may be severe and outstanding symptoms in a few cases, they are more usually completely absent except as transitory signs immediately after operation (Cairns and Mosberg, 1951 ; Poppen, Reyes, and Horrax, 1953). These tumours, however, grow from the anterior-superior part of the third ventricle and may occlude the foramina of Monro. The side walls of the ventricle may be subjected to pressure, but the floor usually escapes.

It is the aim of this paper to report further observations which we consider may indicate that specific disorders of memory may arise from focal lesions in the region of the third ventricle. Between June, 1950, and June, 1952, 180 patients in whom intracranial lesions were verified at operation,

necropsy, or by encephalography in the Nuffield Department of Surgery, were subjected to psychological investigations designed to elicit signs of gross memory defects where these existed. Whenever possible mental tests adapted from the Wechsler, Babcock, or Binet scales were also given, but these usually had to be modified to the individual circumstances.

The data obtained from this investigation have been analysed from three aspects: (1) Special attention has been given to those patients in whom both memory disturbances and site of lesion were well defined and carefully studied. (2) The incidence of memory disorders in lesions involving different cerebral areas has been estimated and compared. (3) Those patients who showed profound and specific memory disorders have been separated from the others and compared as regards the site of the lesion.

Cases of Well Defined Memory Disturbance and Site of Lesion

Only four of the 180 patients interviewed could be included in this group, and they will be described in detail.

Case 1.—F. T., a mechanical engineer aged 50 (R.I. No. 125648/50), was admitted to the Radcliffe Infirmary on June 3, 1950, complaining of deterioration of vision for two years, excessive sleepiness for 22 months, loss of libido, right frontal headache, and failing memory for two months. It appears that two years previously he had gone to see a specialist in Canada who found evidence of chiasmal compression. This was explored, but no abnormalities were detected. His eyesight failed to improve, but his general health remained fairly good until the onset of headache and sleepiness which prompted him to seek further advice.

On admission he was found to be a healthy, robust-looking man, cooperative but drowsy. He would spend most of his time sleeping, but roused easily and then appeared to be rather disinhibited. The neurological examination revealed slight bilateral primary optic atrophy, with a bitemporal field defect and reduction of visual acuity to finger counting in the right eye and J.14 in the nasal field of the left eye. There were no other abnormalities. Radiographs of the skull were normal, but an air encephalogram showed a large ovoid tumour virtually filling the third ventricle. An electroencephalogram showed that general slowing of the alpha rhythm to 7–8/sec. was the most prominent feature, but this was inhibited on opening the eye. He showed some 4/sec. groups frontally on over-breathing and also a small amount of 14–16/sec. activity—possibly connected with his drowsiness.

Mentally, he was fully orientated in time and space and had some insight into his disturbances. He was able to give a coherent account of his past and of the events leading up to his admission. On memory tests it was found that, although immediate memory span was normal as judged by sentence repetition, learning ability was severely impaired. Delayed recall was also defective. After the lapse of 12 hours he had little recollection of the tests he had been given. If the original material was presented to him again, he might claim it as familiar, but overestimated the time since its previous presentation. He also tended to confabulate. Intellect and judgment appeared well preserved.

On June 19, 1950, a craniopharyngioma in the third ventricle was removed by a right transventricular approach. He came round from the operation an hour or two after returning to the ward and was very bright—a little disorientated, but talking sensibly. The following day he was noted to be outstandingly euphoric. He was also inclined to be restless and to get out of bed, and he began confabulating in earnest. He retained correct orientation in time and space, but mistook hospital personnel for his relatives, told stories of long telephone calls he believed he had made since his operation, and described a number of other fictitious experiences. He was still able to describe correctly events leading up to his admission to hospital, but was unable to recall test material presented to him either before or since operation.

Over the succeeding few days he continued to show the same mental condition with little insight into his disturbances. He believed he was improving daily and that his memory was almost perfect.

On June 25, 1950, he appeared to regain some insight into his delusions and was able to accept a suggestion that the peculiar events he described might be imaginary. None the less, he continued to confabulate new stories. Perception and judgment were also much impaired. Although able to name the pictures on the Wechsler Picture Completion Test, he failed to appreciate any of their missing pieces and was unable to recall any of the pictures a few minutes later.

On June 29, 1950, eight days after operation, he began to get up and about the ward. He appeared at first to have little recollection of its geography from his pre-operative experience, but soon learned his way around. As he did so, many recollections of pre-operative events which had been forgotten or denied came back to him.

Over the next few days there was a steady improvement in insight, memorizing, and judgment. New confabulations were absent, and on the Wechsler Similarities Test he produced a score equivalent to an I.Q. of 135. However, although he was able to remember the majority of tests from one day to the next, he still showed some uncertainty of memory.

He was discharged on July 5, 1950. Apart from his visual acuity, the field defects, and the loss of libido, none of which had improved, he had no cranial nerve deficiencies, and the motor and sensory functions were normal. The headaches and drowsiness of which he had complained on admission no longer worried him, and his memorizing had so improved that he showed no defects on formal testing.

Unfortunately, the patient returned to Canada soon

after his discharge, so that opportunities for follow-up studies were not available.

Case 2.—E. S., a schoolmistress aged 51 (R.I. No. 147029), was admitted to the Radcliffe Infirmary on October 24, 1951, after transfer from a mental hospital where she had been for about six weeks as a voluntary patient. The history was supplied by her family and by a sister from a neighbouring convent where she had been staying at the onset of her illness. According to her family, the patient had always shown some peculiarities of personality, but she was able to look after herself, earn her own living, and had travelled widely. She was in the habit of spending some months each summer in retreat in the convent where she was taken ill. Nothing abnormal had been noted about her until about three months before her admission to hospital, when she had had several lapses of memory and it was decided that she should resign her teaching job.

During the week before her admission to hospital she became confused and disorientated. On September 3, 1951, she complained of a headache and was told to lie down. On September 6 she vomited and became drowsy, and the belief that she had been taking drugs led to her admission to hospital.

During the week following her admission to the mental hospital the patient vomited once or twice a day. Her pulse remained at about 60, but there were no neurological signs. She was transferred to the Churchill Hospital for further investigation, and two air encephalograms were performed, both with equivocal results. On physical examination she was an obese middle-aged woman, and her mental state was such that it was difficult to carry out a full neurological examination. There was no anosmia, the optic discs were pale (but she was highly myopic), and no definite field defect could be demonstrated on confrontation. There was possibly a slight relative weakness of the right limbs, but it was very slight, and there was no alteration in the reflexes, nor any sensory defect. The blood pressure was normal (150-90 mm. Hg) and the general systemic examination was normal. Radiographs of the skull showed no abnormality, but a ventriculogram revealed a considerable hydrocephalus due to a tumour in the third ventricle. The electroencephalogram showed episodes of high-voltage 2/sec. waves, maximal frontally, of the type seen with lesions of the upper brain-stem. In between episodes the alpha was fairly well preserved and mixed with a 16/sec. beta component.

Mentally, the patient was drowsy, but wakened easily and would remain awake so long as her attention was being occupied. She was disorientated for time and place, apparently believing herself to be near her home, but realizing at the same time that her immediate surroundings were unfamiliar. Her manner was blusteringly jovial, and her social responses were fairly well preserved. On tests of reasoning and abstraction she still showed considerable ability, but on tests of free association she showed concreteness, her responses consisting chiefly of rhyming or completion words (e.g., red—fed ; grass—brass ; pale—pink).

Memory tests revealed a high degree of amnesia for recent and remote events. To direct questioning she was able to give a few outstanding facts, without details, about the last world war and about her personal past, but they were very much confused. Immediate memory span, as measured by repetition of digits, was about average, but learning and delayed recall were extremely poor. Test material, if recognized, was displaced in time and referred to the wrong contexts. There was little apparent disturbance of speech, but there was some dyslexia and dysgraphia ; she was fully continent.

At operation on October 25, 1951, a craniopharyngioma in the third ventricle was partially removed.

On returning to the ward the patient's general condition was good. An hour later she was able to answer questions. The following morning she appeared to be in much the same mental condition as before operation, except for her speech. Although this was fairly fluent and well formed, she seemed to have some difficulty in finding words, and her sentences were confused. She was grossly disorientated in time and space. She appeared to believe that she was still working in a school, and she confabulated freely.

The following day she was less well. She answered questions more slowly and only after long pauses. There was much oedema of the face and around the wound. Lumbar puncture showed blood-stained fluid at a pressure of 450. Her temperature was 101° F. Reduction of lumbar puncture pressure caused a slight improvement in responsiveness, but she was no less confused. She became progressively less responsive and died three days later.

At necropsy, examination of the base of the brain revealed a yellowish cystic tumour, apparently arising from the upper part of the stalk of the pituitary gland, and largely filling the floor of the third ventricle. On sagittal section the tumour was seen to occupy the floor of the third ventricle, projecting forward above the

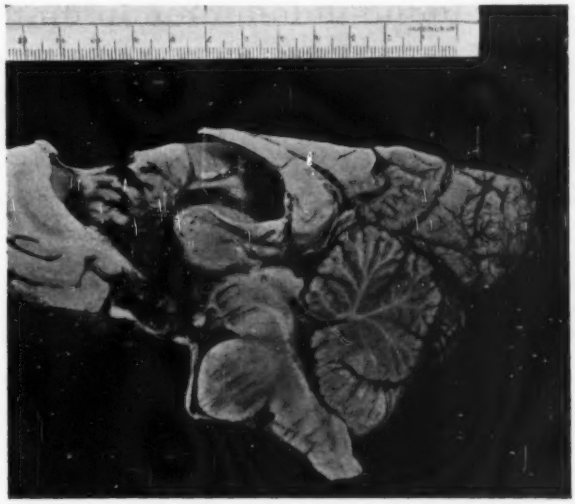

FIG. 1.—Median sagittal section of brain showing tumour (craniopharyngioma) in the floor of the third ventricle.

optic chiasm (Fig. 1). It measured 2 cm. from before back × 1 cm. from above down × 2 cm. from side to side. The dark area above this is the operative cavity in the anterior part of the third ventricle. Both pillars of the fornix were divided at operation. There was a moderate internal hydrocephalus.

Histologically the tumour had all the features of a craniopharyngioma.

Case 3.—D. W., a woodwork machinist aged 63 (R.I. No. 157481), was admitted to the Radcliffe Infirmary on May 1, 1952, complaining of headache, falling attacks during which consciousness was occasionally lost, progressive failure of memory for about 18 months, together with some failing vision more recently. There was also a history of recent excessive thirst.

On physical examination he was a tall, obese man, with a smooth skin and scanty pubic and axillary hair. Genital development was normal. There was bilateral papilloedema, a bitemporal field defect, and reduction of visual acuity to 6/9 J.16 on the right, 2/60 and finger counting on the left. There were no other neurological defects. Radiographs of the skull revealed some enlargement and erosion of the sella turcica with a good deal of calcification above it.

An electroencephalogram showed a poorly represented alpha rhythm, a dominant frequency of 6/sec., and diffuse slow activity. Episodes of high-voltage 1–2/sec. waves were prominent in the left temporal leads.

Mentally, he was drowsy, but always roused easily and cooperated willingly. He was, however, extremely distractable and easily fatigued, so that the examination had to be carried out in a series of short sessions, during each of which he gave the impression of being slightly disinhibited and emotionally labile.

He was fully orientated in time and space and could give a detailed account of his past, including the events leading up to his admission ; but his performance on simple tests of general knowledge suggested that there was some impairment of memory for well established learning.

Intellect appeared to be a low average, and his immediate memory span, as measured by retention of digits, was small. There was also some impairment of learning and of delayed recall.

On May 8, 1952, a ventriculogram was performed. Pressure was 170 mm. and the ventricle communicated freely, probably through a patent septum pellucidum. The radiographs showed considerable symmetrical hydrocephalus due to occlusion of the third ventricle by a large spherical tumour. The ventriculogram was followed by cerebellar decompression and ventriculocisternostomy. The operation was well tolerated, and the following morning he appeared alert and comfortable.

During the first post-operative week the patient was very drowsy and became truculent when roused. It was difficult to gain his cooperation on formal tests, although the responses that he did give indicated slight further deterioration of intellect and further gross memory impairment. Orientation fluctuated, apparently with his degree of wakefulness. He had difficulty in keeping track of the time, and on several occasions maintained that the ward in which he was now being nursed was a different one, although similar, from that in which he had been before. He was never, however, in any doubt about being in Oxford.

His performance on the same tests as those conducted before operation showed that memory span was little affected, but learning and delayed recall were markedly impaired.

He was restless, being inclined to get out of bed two or three times a day for no reason, and incontinent.

Physical examination during this first post-operative week showed improvement of vision, especially in the left eye, and a subsidence of the papilloedema. At lumbar puncture it was found that during the first few days after the operation the fluid was bloodstained and at a pressure of 240–300 mm. Hg. This improved, but by May 25, 1952, the skin at the site of the wound became red. A low-grade inflammation of the posterior fossa was suspected, and he was put on a course of sulphadiazine with good results.

During the following week there seemed to be a slight deterioration of alertness. His responses to verbal intelligence tests were of a poorer quality even than before, and he was also unable to say how he had come into hospital and what he had been doing before his illness. He maintained that he had left the Radcliffe Infirmary and was now living near his niece in Scotland. He usually recognized hospital personnel, however, although he was not able to remember their names.

On June 3, 1952, about 10 ml. of yellow fluid was withdrawn from the cystic part of the tumour by needle through a right frontal burr-hole. After this he appeared to become a little more alert, but there was little improvement in his confusion, disorientation, or memory. His speech was brisker, but still rambling, and he was now unable to say (without looking) what he had on his bedside locker.

By June 10 he was noted to be much more awake and showed signs of confabulating for the first time. He was sitting up in a chair for part of each day.

During the next few days the tendency to confabulate increased, together with alertness, responsiveness, and apparent improvement in intellectual control. But the memory defects remained as gross as before and therefore became more obvious. When taken by an attendant for walks about the corridors he would be quite unable to find his own way back to the ward ; he denied that he had ever slept in the hospital, failed to recognize hospital personnel (or misidentified them with former acquaintances), and refused to own any of the possessions in his bedside locker.

On July 1, 1952, still presenting the above picture, he was transferred to another hospital (Royal Berks) for further observation.

Case 4.—G. P., a farm labourer aged 22 (R.I. No. 111669/49), was admitted to the Radcliffe Infirmary on September 10, 1949, complaining of drowsiness during the past six months and vomiting and frontal headaches for four days. He had been unable to work for the

preceding three months, and three days before admission had been sent home from the lodgings where he lived as he could not keep awake. His relatives reported that he had been excessively thirsty for the last year or so and had admitted to lack of libido.

On admission, he was a small man, with a smooth chin and hairless skin, and pronounced genital hypoplasia. He was very drowsy, but could be roused to cooperate in a modified examination. There was no papilloedema, nor did there appear to be any hemianopia. The pupils and ocular movements were normal, and the only definite neurological defect was a slight left hemiparesis with a corresponding alteration in the reflexes. The blood pressure was 90/70 mm. Hg. Radiographs of the skull showed a good deal of calcification in and above the sella turcica, the appearances being characteristic of a craniopharyngioma.

Mental examination revealed that he was very drowsy but rousable by speech and by painful stimuli. His memory was not tested. Later that evening he went into coma. At operation a left frontal burr-hole was made and the ventricular pressure was found to be over 600. After this was relieved the patient once more responded to speech.

Three days later he became drowsy and unresponsive again, and was lying in a typical decerebrate posture. Ventricular tapping did not alter his condition, but after the removal of 33 ml. of fluid from a suprasellar cyst the patient recovered to the extent of responding to speech again. By the following morning he was alert and orientated. He could give his personal history and remember what he had had for breakfast. The electroencephalogram, which before operation had shown a preponderance of slow waves, came back to normal more slowly.

The patient remained well for a few days, but on September 18 he began to get drowsy again. Ventriculocisternostomy was performed on September 19, but although it appeared to deal adequately with the pressure situation the patient's mental state remained unaltered.

On October 1 the cyst was tapped again, with the removal of about 10 ml. of fluid. After this the patient's mental condition improved somewhat. He became alert, and slightly aggressive, and was noted to present features typical of Korsakov's psychosis. He was disorientated for time and place and could not find his way back to his bed after leaving the ward. He was unable to recall day-to-day events, such as what he had had for meals, the visits of doctors, etc., and he was easily led to confabulate about his recent past. He slept a good deal, but roused easily. Occasionally he was incontinent.

These defects gradually cleared up, and on October 17 he appeared to be more or less rational. Three days later, however, he began to get drowsy and confused again, vomiting and confabulating, and showing gross amnesia. On October 23 he collapsed at lunch and was in stupor for some minutes. Later that day ventricular pressure was found to be within normal limits, but the cystic part of the tumour had reaccumulated. After aspiration of 30 ml. of fluid from the cyst the patient's mental condition began to improve. He remained confused and disorientated for the rest of that day, but on the following day there was considerable improvement. When he started confabulating he would pull himself up, look puzzled, and say he knew that something was wrong.

The electroencephalogram, which before aspiration of the cyst had shown large 100 microvolt 1–2/sec. waves typical of coma, showed a rapid return of alpha rhythm ; a good 8–10/sec. appeared at a record taken 10 minutes after aspiration. This continued to improve over 24 hours. The records in this case have already been referred to and illustrated elsewhere (Cairns, 1952).

The patient thereafter had a long and fluctuating illness, during which the above sequence of events was repeated on numerous occasions. On each occasion that the cyst began to reaccumulate the first sign of deterioration was the presence of slow waves in the E.E.G., after which the patient showed signs of becoming drowsy and amnesic. Although usually able to recount his personal history and to repeat an average number of digits forwards and backwards, he would be unable to find his way back to his ward if he left it, but would recognize his bed when he saw it again. He would start to recite poems which he said he knew, but seldom get beyond the first line. After this he would wander from the point and improvise.

Each time that the cyst was successfully aspirated his mental condition improved in parallel with recovery of alpha rhythm in the E.E.G. On two occasions (December 28, 1949, and January 24, 1950) the patient appeared to be so well that he was allowed to go home. The improvement was only short-lived, however, before his mental condition deteriorated and he had to be readmitted. On each occasion ventricular tapping had little effect, but aspiration of the cyst was followed by striking improvement of both E.E.G. and mentality.

After his third admission in January, 1950, he was seen to show some deterioration of personality as well as chronic impairment of memory in the periods of remission. When seen by a psychologist (Miss M. Davidson) on April 16, 1950, he was found to have a vocabulary level up to that of an average adult, but severe impairment on a wide range of memory tests involving orientation and the ability to keep the goal in view.

As the patient appeared to be losing ground, it was decided to try a more radical operation. An attempt was made on June 1, 1950, to drain the cyst into the ventricle, but the patient never fully recovered from the operation and died three days later.

At necropsy there was a nodular cystic tumour covering the base of the third ventricle. It measured 4·5 mm. from before back × 2·5 cm. from side to side × 2·5 cm. from above down. Anteriorly it was in contact with the optic chiasm, and the cerebral peduncles were stretched over its lateral margins. In a mid-sagittal section of the brain tumour could be seen to occupy the floor of the third ventricle and the interpeduncular space (Fig. 2). This part of the tumour was solid : the collapsed cyst could be identified on its upper surface in the lower part of the third ventricle. Coronal sections showed that the tumour invaded the antero-inferior part of the left

FIG. 2.—Median sagittal section of brain showing tumour (craniopharyngioma) in the floor of the third ventricle and interpeduncular fossa.

thalamus. There was a moderate internal hydrocephalus.

Microscopic examination of the tumour showed it to be a craniopharyngioma.

Mental Aspects.—Each of the four cases described here exhibited the mental picture of Korsakov's syndrome, consisting of some impoverishment of intellect, changes of personality (usually euphoria or apathy), disorientation, confabulation, and impairment of memory. Since it is the last which is the chief concern at the moment, the other defects may be temporarily disregarded.

The memory defects consisted of (*a*) inability to retain new impressions for any length of time; (*b*) inaccessibility of memory for past experiences; (*c*) distortion and fractionation of recent memory; (*d*) inability to learn new sensorimotor habits. Immediate memory span, as measured by repetition of digits or sentences, was comparatively well maintained in all patients.

Site and Extent of Lesion.—In each of these cases there was a well defined lesion involving the floor and sides of the third ventricle. In Cases 1 and 2 there was no evidence of pressure on other areas of the brain, and in Cases 3 and 4, where intracranial pressure was originally high, this was relieved without affecting the amnesia.

Incidence of Memory Disorders in Third Ventricle Tumours

Although in the four cases quoted above the mental disturbances and site of lesion were strikingly uniform, doubts may be felt regarding the frequency of such instances. How often are similar mental pictures seen in association with such lesions, and how often are such mental pictures seen in lesions involving other areas of the brain? In order to answer the first of these questions it was decided to examine the notes of all patients in the Nuffield Department of Surgery treated for craniopharyngiomas. Thirty-two cases were found, in 21 of which the tumour involved essentially the areas round the floor and sides of the third ventricle. In the remaining 11 the tumour was situated further forward and was difficult to distinguish in symptoms and appearance from a pituitary tumour.

The notes of these 32 cases were examined closely for evidence of memory disturbances, and the distribution of patients according to whether or not such evidence was present is shown for the two types of tumour in Table I. It will be seen that

TABLE I

DISTRIBUTION OF PATIENTS WITH CRANIOPHARYNGIOMAS ACCORDING TO LOCALIZATION OF TUMOUR AND DEGREE OF MEMORY DISTURBANCE

Age in Years	Third Ventricle Syndrome				Chiasmal Syndrome			
	No. of Patients	Memory Disturbance			No. of Patients	Memory Disturbance		
		Severe	Moderate	None		Severe	Moderate	None
0–20	7	0	3	4	6	0	0	6
21–40	6	2	3	1	2	0	0	2
41–60	8	6	1	1	3	0	0	3
Totals	21	8	7	6	11	0	0	11

whereas nearly three-quarters, or 0·72%, of the patients with tumours involving the third ventricle showed some degree of memory impairment, there was not a single such case among the group in which the tumour was further forward. The frequency of mental symptoms was higher in the older groups, but some impairment was also seen in nearly half the children. Thus it appears that the memory defects cannot be specific to the type of lesion, but are associated with its localization.

In order to substantiate these conclusions the records of a number of other patients with discrete third ventricle tumours—other than craniopharyngiomas—were also examined, and the findings agreed closely with the above. However, there was also some degree of either raised intracranial pressure or hydrocephalus in each of these cases, so that it may well be suspected that the memory disturbances associated with tumours of the third ventricle were due to generalized cerebral derangement rather than to local pressure.

In Cases 1–4, described here, the possibility of the mental symptoms being due to raised intracranial pressure was virtually ruled out, but it was decided further to compare the incidence of memory disturbances in the third ventricle tumours with that in posterior fossa tumours.

Among the patients admitted to the Nuffield Department of Surgery between June, 1950 and 1952, there were 24 patients aged between 10 and 60 with verified tumours of the posterior fossa, and evidence that intracranial pressure had been raised at some period during their illness. The incidence of memory disturbances in this group of patients is shown in Table II. In comparison with the high

TABLE II

DISTRIBUTION OF PATIENTS WITH POSTERIOR FOSSA TUMOURS ACCORDING TO PRESENCE OR ABSENCE OF MEMORY DISORDER

Age in Years	No. of Patients	Memory Disorder	
		Present	Absent
10–20	2	2	0
21–40	11	3	8
41–60	11	6	5
Totals	24	11	13

proportion of memory disturbances seen in third ventricle tumours (see Table I), under half (0·45%) of the patients with tumours of the posterior fossa show comparable disturbances. The fact that some of them do so does not necessarily argue against the hypothesis that amnesia is associated with disturbance in and around the third ventricle, because posterior fossa tumours not infrequently cause physical disturbances commonly referred to the third ventricle. Thus, it is well known that posterior fossa tumours often lead to amenorrhoea, impotence, diabetes insipidus, and other physical manifestations of hypopituitarism and hypothalamic disturbance. These are the effects of dilatation of, and increased pressure in, the third ventricle, which are the common results of posterior fossa tumours.

As in the craniopharyngiomas, it was found on further analysis of the 24 cases with posterior fossa tumours that the incidence of mental disturbances was higher among the older patients than among the younger ones (see Table II). The implication of this will be discussed later on.

The Site of Lesions Associated with Impaired Memory

Of the 180 patients studied during this investigation, a large proportion of those showing mental impairment was found to exhibit specific disabilities such as dysphasia, dysarthria, spatial disorientation, apraxia, etc. There were only 26 patients in whom it was felt that memory impairment was the outstanding mental defect. In many of these cases the tumours were infiltrating and precise localization could not be given with certainty. However, the predominant site of lesion in each of these 26 cases was estimated, and the frequency for each site is shown in Table III. It will be seen that more cases have deep mid-line lesions than have lesions in all other areas of the brain together.

TABLE III

DISTRIBUTION OF PATIENTS WITH SPECIFIC DISTURBANCES OF MEMORY ACCORDING TO PREDOMINANT SITE OF LESION

Area of Lesion	Posterior Fossa	Right Hemisphere	Left Hemisphere	Mid-line, Deep	Mid-line, Cortical	Frontal
Number of patients (out of 26)	4	0	3	15	0	4

It should also be mentioned, however, that the mental pictures were not identical in all these cases. In the four posterior fossa cases the patients showed considerable retardation and dementia as well as amnesia, and it was difficult to say how much of the memory defect was due to these factors. In the three left hemisphere lesions there was some speech disorder, which made mental testing unreliable, and in the frontal cases there was gross perseveration and fatuousness and the patients gave the impression that they were not bothering to remember rather than that they were unable to do so. In the 15 cases of deep mid-line lesion, on the other hand, the patients were often drowsy and apathetic if unstimulated, but once roused were alert, cooperative, and capable of considerable intellectual activity, although grossly amnesic and sometimes even showing the complete Korsakov syndrome.

Discussion

From whatever aspect the material reported here is analysed, it indicates that impairment of memory is most frequent, pronounced and specific when the area of the brain surrounding the floor and sides of the third ventricle is damaged. Speaking generally, lesions further forward, in the frontal area, often result in the patients not bothering to use their memories, while lesions of a cerebral hemisphere may cause loss of memory for particular skills, but the patients remain capable of remembering events ; lesions of the posterior fossa may make the patients

retarded and depressed and unable to think of remembering. With lesions in and around the third ventricle, however, the patients frequently retain good personality and intellect but show gross defects of memory. The loss is not for particular events, nor for immediate appreciation of impressions, it is rather for their normal endurance and retention.

Apart from the site of the lesion, however, it is possible that other factors may be involved in determining the memory disturbance, so that the relationship between these factors and amnesia should be considered.

Increased Intracranial Pressure.—Evidence suggesting that memory disturbances are due to a generalized cerebral derangement has already been discussed, and the frequency of raised intracranial pressure in cases of tumour of the third ventricle raises the possibility that the amnesia noted in these cases may be the result of secondary disturbances of a more generalized nature. This hypothesis has already been considered and rejected by Busch (1940), and the observations reported here support his conclusion. In the four cases described in detail—and Case 4 in particular—intracranial pressure was reduced to normal without affecting memorizing. Conversely, in the cases of posterior fossa tumour, in which intracranial pressure was invariably raised, the incidence of memory disturbances was smaller and usually of a different nature from that in those of third ventricle tumour.

Relationship with Other Psychological Defects.—The presence of at least some disturbances in association with severe memory defects—such as apathy, dementia, disorientation, confabulation—raises the possibility that the memory defects may themselves be secondary to disturbances in some of these other mental spheres. However, comparison between the mental state seen in the patients with third ventricle lesions and that in patients with lesions in other areas of the brain, indicates that this is unlikely to be the case. The patients with posterior fossa tumours showed considerably greater apathy and dementia in relation to amnesia than did those with lesions around the third ventricle; and patients with frontal lobe lesions showed considerably more in the way of personality changes. Thus, the disturbances of memory, though they may coincide with other mental disorders, cannot be considered as primarily due to them.

Relationship to Age at Time of Onset.—In agreement with Walther-Büel (1951) and Bleuler (1951), it was noted here that memory disorders are more common in older people than in younger ones. However, from this finding it does not necessarily follow that the amnesic reaction is independent of the cerebral area involved and due only to the patient's age at the time of illness. A similar association is found to occur between the degree of mental impairment and age at the time of lesion in other functional areas of the brain—notably the temporal lobe—without this association being taken to imply that the locality of a lesion in adults is unconnected with its mental sequels.

Lowered Level of Consciousness and Somnolence.—As shown by the E.E.G. recordings of the individual cases reported here, impairment of memory was closely related to generalized lowering of cortical activity.

These conclusions suggest that memory is as much, if not more, a function of generalized wakefulness and consciousness as it is of intellect, personality, or mood. The exact mechanism by which the functions are connected and conducted, however, is still unexplained. Although the evidence presented above has little to offer in this respect, it does suggest that further study of the functions of the area round the third ventricle is well worth while, as it might yield especially valuable information about the connexion between mental and cerebral activity.

Summary

One hundred and eighty patients with verified intracranial lesions have been interviewed by psychologists in a neurosurgical unit in order to ascertain whether there is any area of the brain the destruction of which is specifically associated with impairment of memory.

The data obtained have been analysed from three aspects: (*a*) Four cases in which impairment of memory and site of lesion were clearly defined and well localized are described in detail; (*b*) the incidence of memory disturbances in tumours of the third ventricle has been compared with that in other well localized intracerebral tumours; (*c*) patients with obvious and clear-cut defects of memory have been examined for the most common site of lesion.

All analyses support the conclusion that memory impairment is most common and specific when the area surrounding the floor and walls of the third ventricle is disturbed.

The relationship between memory disturbances and other possible causal mechanisms is briefly discussed.

We would like to acknowledge our indebtedness to the late Sir Hugh Cairns for the initiation and thesis of the above work and for valuable guidance during the earlier part of the investigations ; also to Miss M. Davidson for the psychological assessment of one patient and Miss M. Taylor for E.E.G. records and interpretations.

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THE FEBRUARY (1954) ISSUE

The February (1954) issue contains the following papers :—

Traumatic Epilepsy after Closed Head Injury. Gilbert Phillips.

Demonstration of ^{82}BR in Nerve Cells. Sven-Olof Brattgard and Torsten Lindqvist.

Frontal Lobe Wounds Causing Disinhibition. A Study of Six Cases. Hugh F. Jarvie.

A Histological and Chemical Study of Three Cases of Diffuse Cerebral Sclerosis. W. Blackwood and J. N. Cumings.

Post-encephalitic Parkinsonism with Amyotrophy. J. G. Greenfield and W. B. Matthews.

A Study of Eight Surgically Treated Cases of Spontaneous Sub-cortical Haematoma. Aloys Werner.

Dimercaprol in the Pre-neurological Stage of Wilson's Disease (Hepatolenticular Degeneration). C. G. Warnock and D. W. Neill.

Studies of the Connexions of the Fornix System. H. M. Daitz and T. P. S. Powell.

The Treatment of Dystrophia Myotonica with A.C.T.H. Oliver Garai.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1954, **17**, 124.

VARIATIONS WITH AGE IN THE NUMBER OF ACTIVE PALMAR DIGITAL SWEAT GLANDS

BY

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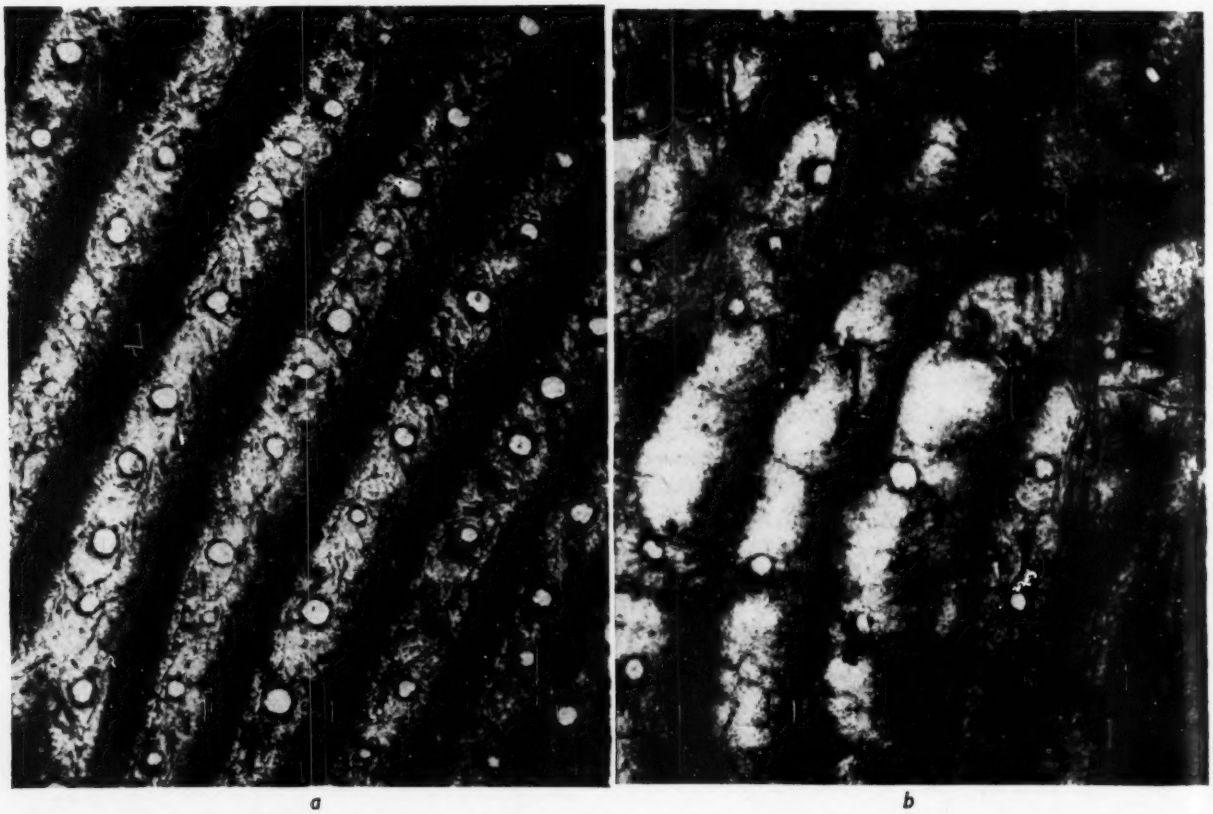
Acute emotion to which a response is made has been found to result in an increase of palmar sweat activity (Kuno, 1934), but tensional states in which responses are suppressed result in a decrease in activity (Van der Valk and Groen, 1950). This psychosomatic function of the palmar sweat glands can be recorded either by electrical skin resistance or by direct sweat prints, and is now being increasingly used in psychiatry (Bitterman and Holtzman, 1952; Van der Valk and Groen, 1950; Seitz and Shipley, 1952).

Palmar sweat activity is an indicator not only of these emotional changes but also of autonomic activity, and sweating tests have also been used in neurology (Regelsberger, 1949; Malis, Grynbaum, and Bierman, 1949), proving useful in the diagnosis of early nerve lesions (Kahn, 1951).

Accurate assessment of the information obtained from these tests is not possible unless the gerontological effect on palmar sweating is taken into account.

The object of this paper was to investigate this effect statistically.



a *b*

FIG. 1.—Plastic impressions of finger pad in (*a*) boy aged 15 years and (*b*) man aged 88 years showing " pores " of active sweat glands (both × 50).

Method

Records of active sweat glands in the pad of the right middle finger were obtained from 123 healthy males comprising 20 schoolboys, 54 firemen, and 49 Chelsea pensioners. The age range was 7 to 96 years.

The technique used was that of Sutarman and Thomson (1952). The pad of the right middle finger was blotted carefully to remove excess sweat and a layer of plastic paint applied ; this dried within a few seconds and was removed by the application of a strip of " sellotape ". The paint held a record of the finger print, active sweat glands showing as " pores " along the ridges (Fig. 1).

Every subject was seated for half an hour before and during the test which took place between 2.15 and 3.15 p.m. The object and procedure of the tests were explained to eliminate as far as possible any emotional tension. Room temperatures varied between 60° and 67° F. with an average of 65° F., except for subjects in the sixth decade for whom it was between 67° and 73° F. ; relative humidity varied between 48% and 55% with an average of 50%.

Counts of the number of active sweat glands in a unit area of 4 sq. mm. immediately distal to the central whorl were made under a magnification of 10. This area was constantly used because of variation in the number of glands from area to area (Randall, 1946).

Owing to the fact that skin stretches with growth, the number of sweat glands in a unit area of skin in the first two decades will be falsely high compared with the number after growth has ceased, and for this reason a correction was made to the figures of the first two decades as follows :

Heights and weights of all subjects were taken and their surface area calculated ; each count was then multiplied by the surface area of the subject and divided by the surface area of an average adult male (1·73 sq. m.), it being presumed that the surface area of a finger increases with growth to the same extent as the rest of the body.

Results

The table contains counts of the number of active sweat glands in the unit area of 123 males, arranged in single columns containing two consecutive decades. In addition it contains the arithmetic mean for each two consecutive decades and their standard deviations. It shows considerable variation between individual counts as well as a decrease in the average counts between each two consecutive decades.

Fig. 2 depicts the arithmetic means of the counts for each two consecutive decades in graphic form. It shows that the counts fall from a maximum of 100 during the first and second decades to a minimum of 14 in the ninth and tenth decades, almost half the drop occurring between the first and second, and third and fourth decades. Statistical significance was shown between the means of each two consecutive decades in that their difference was found to exceed twice the standard error of their means (Hill, 1950).

TABLE

NO. OF ACTIVE SWEAT GLANDS IN 4 SQ. MM. OF PAD OF RIGHT MIDDLE FINGER IMMEDIATELY DISTAL TO CENTRAL WHORL IN RELATION TO AGE

1st and 2nd Decades		3rd and 4th Decades		5th and 6th Decades		7th and 8th Decades		9th and 10th Decades	
Age	Counts	Age	Counts	Age	Counts	Age	Counts	Age	Counts
7	121	23	97	40	63	60	30	80	56
8	149	24	63	40	47	60	59	80	29
9	100	24	88	40	23	63	10	80	34
10	126	25	68	41	49	65	35	80	4
11	73	25	139	42	27	65	24	81	37
12	43	26	108	43	61	66	10	81	13
13	100	26	58	43	53	66	15	82	9
13	148	27	68	44	35	67	33	83	16
13	144	27	50	44	49	67	71	83	13
13	107	27	60	44	43	67	11	84	13
14	102	28	29	45	45	67	12	84	8
15	9	28	14	45	75	68	104	85	13
15	103	29	79	46	15	69	16	87	4
15	90	29	59	46	31	69	7	87	20
15	92	30	78	47	47	70	11	88	31
17	112	31	66	48	59	70	23	89	16
17	144	31	67	48	12	72	54	89	8
17	96	31	54	48	22	72	7	90	24
18	85	31	21	49	6	73	4	90	4
18	45	32	71	52	50	74	76	96	4
—	—	32	19	53	28	75	11	96	0
—	—	34	4	56	65	75	45	—	—
—	—	34	79	58	82	76	18	—	—
—	—	35	84	59	39	77	9	—	—
—	—	36	27	59	39	77	16	—	—
—	—	56	58	—	—	78	5	—	—
—	—	38	27	—	—	79	22	—	—
—	—	38	56	—	—	79	10	—	—
—	—	39	28	—	—	—	—	—	—
Means	100	59		45		27		14	
S.D.	42	33		15		20		17	

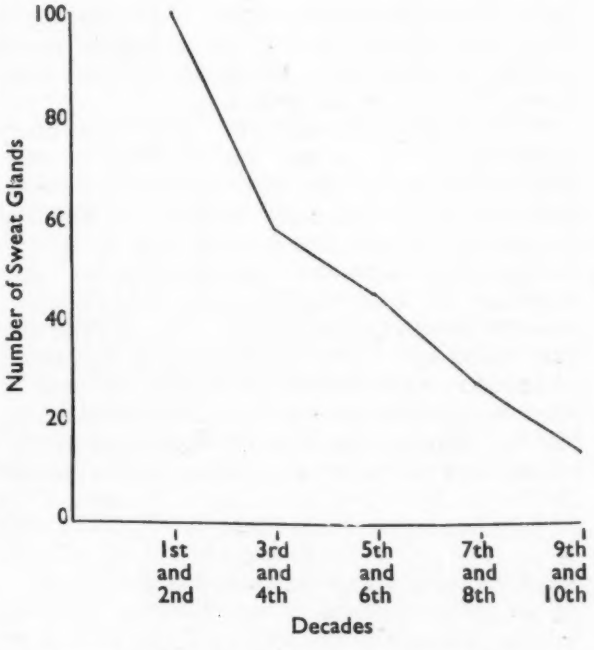


FIG. 2.—Average number of sweat glands for each two consecutive decades.

Discussion

Burch, Cohn, and Neumann (1942) investigated the rate of water loss from the finger tips in eight senile persons and found it to be considerably lower than in younger persons ; this they ascribed to the reduced physiological activity of senility. Van der Valk and Groen (1950) also reported a decreased activity with age, but neither of these authors noted the rapid decrease which occurs in the early decades.

Reduced physiological activity of old age is dependent on several factors, the most important of which are decrease in blood supply, degeneration of the nervous controlling mechanism, and intrinsic degeneration of the glands, the last factor being a constant feature of all organs in senility.

Decreased blood supply occurs with advancing atherosclerosis or with vasoconstriction coincident upon a lowered basal metabolic rate and body temperature. But constriction of the blood supply to an arm has been shown to have no constant effect on palmar sweating (Richter and Whelan, 1943) and List and Peet (1938) have stated that sweating is not dependent on the normal circulation of the blood. It appears unlikely, therefore, that a decreased blood supply to the glands would have any great effect on activity, especially in the early decades.

Degeneration of the nervous controlling mechanism of the glands occurs and has been described in the cerebrum (Riese, 1946), spinal cord (Gardner, 1940), and ganglia of the sympathetic chain (Kuntz, 1938). Subsequent degeneration of the nerve cell fibres with resultant fibrosis would lead to fewer impulses reaching the sweat glands and therefore decreased activity as age progresses.

These factors, although they contribute to a decreased activity in the later decades, do not explain the reason for the maximum rate of decrease occurring during the early decades. A possible explanation of this phenomenon may lie in the activity of the suprarenal cortex, for it has been suggested that a decrease in palmar sweat activity occurs with increased corticoid production (Van der Valk and Groen, 1950 ; MacKinnon, in the press).

During the early decades of life when the body is encountering many new stresses corticoid production will be high, resulting in a rapid decrease of the initially high palmar sweat secretion. In the middle decades an adaptive reaction to constant stresses occurs (Selye, 1950) modifying the suprarenal cortical output, which in turn may modify the steep decline of palmar sweating.

Summary

Counts of active palmar digital sweat glands in 4 sq. mm. of the right middle finger immediately distal to the central whorl were obtained in 123 healthy males under similar conditions.

Counts were shown to be significantly lower between each two consecutive sets of decades, the maximal rate of decrease in numbers occurring between the first and second and third and fourth decades.

It is suggested that (*a*) the maximal rate of decrease in the early decades is due mainly to high corticoid production ; (*b*) that the slower rate of decrease in the later decades is due to a modified corticoid production and a general reduction of physiological activity.

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PHOSPHATE ESTERS IN MYOTONIC HUMAN MUSCLE

BY

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Myotonia congenita is a disorder of the relaxation of skeletal muscle in man. The disease is not accompanied by muscular wasting, and is analogous to a disorder in goats (Kolb, 1938 ; Brown and Harvey, 1939). The affected muscles both of man and goat show similar abnormalities when examined by histological and electromyographic methods. Myotonia becomes apparent during activity after a period of rest. Relaxation is delayed for up to a minute after the first voluntary contraction. With successive contractions the period of myotonic contraction decreases until the muscle eventually behaves like normal muscle.

Electromyographic investigations have suggested that both disorders are due primarily to an abnormally high excitability of the muscle membranes, but it is possible that other factors are operative. Current theories of muscular contraction (Baldwin, 1952) assign an important role to phosphate esters. The patient who is to be described willingly consented to biopsy of small samples of affected muscle to see if they showed abnormalities in the distribution of these esters and thus possibly throw further light on the nature of the disease.

Case Report

The patient was a man aged 42 years, in whom the symptoms of delayed muscular relaxation had been present since early childhood. There was no definite family history of a similar disorder. Myotonia was present regularly after rest, being most evident in the flexors of the fingers, the deltoids, and the quadriceps. A myotonic contraction also occurred on direct percussion of the muscles. This myotonia wore off after repeated contraction ; it was also diminished by quinine. There was no weakness or wasting ; the facial muscles, and in particular the sternomastoids, were normally developed. No cataract could be detected on routine ophthalmoscopy.

Electromyography (Dr. W. D. Fletcher) showed the trains of oscillations characteristic of myotonia when the needle electrode was inserted and on mechanical stimulation of the muscles. After working off the myotonia abnormal oscillations were no longer obtained. Estimations of daily urinary creatine and creatinine excretion were within normal limits.

Results of Biopsies

Two small samples of muscle, about 100 mg., were removed through an incision over the deltoids on each of two separate occasions. The samples were immediately fixed by immersion in a mixture of acetone and solid CO_2 and then extracted with aqueous trichloracetic acid. The extract was analysed for phosphate esters by Caldwell's (1953) adaptation of the chromatographic method of Hanes and Isherwood (1949). The results are given in the Table. Sample 1 was taken from the left deltoid during rest and Sample 2 during a myotonic contraction of this muscle. Sample 3 was taken during a myotonic contraction of the right deltoid, and Sample 4 after the myotonia had been " worked off " by repeated movement of the arm. A sample of resting human muscle from a normal subject (Sample 5) was also examined, and the distribution of phosphate esters in this was very similar to those found by Nevin (1934).

The samples were found to contain, in addition to the usual ester fractions, some of the unidentified fractions which have recently been detected in tortoise muscle by the chromatographic method (Caldwell, 1953). Sample 4, in which the myotonia had been " worked off ", was of particular interest, since, in addition to containing fractions which appeared to correspond to the unknowns C and D found occasionally in tortoise muscles, it also contained an unidentified fraction, unknown F. The distances travelled by unknown F in the two solvents used, were, in terms of that travelled by orthophosphate, 0·65 in n-propanol/ammonia and 0·8 in tertbutyl alcohol/picric acid.

The quantitative findings suggest that the distribution of esters in muscle samples showing symptoms of myotonia is like that in fatigued normal muscle, that is, the creatine phosphate concentration is low and the orthophosphate and monophos-

* I.C.I. research fellow.

TABLE
PHOSPHATE ESTER DISTRIBUTIONS EXPRESSED AS PERCENTAGE OF THE EXTRACTABLE P

Ester	Myotonic Muscle				Normal Muscle
	Showing Signs of Myotonia			Not Showing Signs of Myotonia	
	Sample 1 Resting	Sample 2 during Myotonia	Sample 3 during Myotonia	Sample 4 after Working off Myotonia	Sample 5 Resting
ATP and ADP ..	28·2	28·6	30·9	27·2	34·9
Creatine phosphate	2·3	0·0	16·3	21·6	40·4
Orthophosphate ..	24·7	25·9	27·0	25·2	17·1
Monophosphate esters	27·0	35·1	5·8	0·0	0·0
Diphosphate esters (the value for sample 4 includes unknown D)	12·3	10·4	6·6	2·2	2·8
Unknown A ..	—	—	6·2	5·4	2·8
Unknown B ..	5·6	0·0	7·3	1·2	1·9
Unknown C ..	—	—	—	11·7	—
Unknown F ..	—	—	—	6·1	—
P not extracted by trichloroacetic acid (μg. P/g) ..	232	215	149	124	238

phate esters are high. After the process of " working off" the myotonia, the amounts of creatine phosphate and the monophosphate esters become more like those in normal resting muscle and unidentified esters appear.

Intense electrical activity takes place along myotonic muscle on both nervous and mechanical stimulation, the resulting myotonic contraction being similar to that during tetanic stimulation of normal muscle (Brown and Harvey, 1939). Since all three samples of myotonic muscle would have been stimulated mechanically by the removal of the biopsy material in addition to any nerve stimulation, it is not surprising to find that the amounts of creatine phosphate and monophosphate esters are similar to those found in normal muscle fatigued by tetanic stimulation. After the process of " working off " the myotonic muscle resembles normal muscle in its electrical behaviour. It does not undergo a myotonic contraction on removal of the biopsy material and the amounts of creatine phosphate and monophosphate esters resemble those in normal muscle.

Since the changes in creatine phosphate and the monophosphate esters can be interpreted in terms of the behaviour of these compounds in normal muscle and the electrical properties of myotonic muscle, it is unlikely that they contribute directly to the myotonia. Thus, on this interpretation, myotonia remains entirely a result of the hyperexcitability of the muscle membrane. The significance of the unidentified compounds which appeared after " working off " and any connexion they may have with the condition is obscure.

We wish to thank Dr. E. A. Blake Pritchard for permission to make these observations on this case, and to Dr. A. J. Bowdler for assistance with the biopsies.

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A RARE PRESENILE DEMENTIA ASSOCIATED WITH CORTICAL BLINDNESS (HEIDENHAIN'S SYNDROME)

BY

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In 1929 Heidenhain reported three cases of what he called a peculiar form of presenile disease. In his first case the patient (Eckert), a man aged 55, after an attack of influenza, began to suffer from headaches, sleeplessness, and fleeting limb pains. His vision deteriorated rapidly and he became demented. Other signs of the disorder included dysarthria, ataxia, athetotic movements, and a rigidity of all four limbs without signs of pyramidal disorder. He became blind, but the discs and fundi showed no abnormality. He died four months after the onset of his symptoms. The cerebrospinal fluid had been normal throughout the illness, the Wassermann reaction in both blood and spinal fluid being negative. In his family, one brother had died from a cerebral disorder following pneumonia, but no further details were known.

At necropsy there was severe atheroma of the coronary arteries and brown atrophy of the heart. The brain weighed 1,470 g., the basal arteries were atheromatous, and the leptomeninges were thickened over the frontal convexities and around the Sylvian fissures. There was more than the usual amount of cerebrospinal fluid in the subarachnoid spaces, but there was no conspicuous convolutional atrophy.

The histological investigation of the brain showed changes in the cerebral cortex which were most marked in the occipital lobe, less severe in the parietal cortex, the posterior insula, and the first temporal convolution, and practically absent in the precentral and frontal regions. The Betz cells were normal. The changes in the occipital lobe (including the calcarine region) consisted of shrinkage and pigment atrophy, particularly of the small nerve cells in layers 4, 2, 6 (in that order), a disturbed cytoarchitecture and marked proliferation of protoplasmic and fibrous astrocytes. Some nerve cells were swollen, others gave an appearance resembling Nissl's severe cell change. There was no demyelination. In Bielschowsky preparations senile plaques and neurofibrillary tangles were absent. The blood vessels were healthy and there was no inflammation. The white matter was normal except for a small amount of subcortical glial proliferation. Within the striate body the large nerve cells were unaffected while the small cells showed some non-specific degeneration. The nerve cells of the globus pallidus, the grey centres in the mid-brain, pons, medulla, and cerebellum were normal.

In his second case (Bleder), a man of 53 developed a rapidly progressive dementia with echolalia and perseveration, deterioration of vision with photophobia, vertigo, intention tremor, grasp reflex, athetosis of the upper limbs, and in the later stages severe generalized rigidity without signs of any pyramidal tract lesion. Blood and cerebrospinal fluid were normal. He became blind and died four months after the onset of the disease from terminal septicaemia and cardiac failure. The discs and fundi were normal throughout his illness. In the family history one brother had committed suicide in the course of an affective mental disorder, and the patient's daughter was reputed to have died from epidemic encephalitis.

Necropsy showed a brown atrophy of the heart, old healed pulmonary tuberculosis, and severe ulceration of the skin covering the anterior surface of both knees. The brain weighed 1,290 g. No macroscopic change was seen.

Histological investigation revealed changes similar to those found in the previous case, but of greater severity. The occipital lobe, including the calcarine region, was again the most severely affected portion of the brain. All cortical layers were involved, particularly the fourth layer. A finely meshed status spongiosus was present, chiefly affecting the upper layers of the occipital cortex. The glial reaction was similar to that in the first case. The parietal region, and in contrast to Case 1, the precentral and frontal regions were also involved. The temporal lobe was less affected, the cornu Ammonis being quite normal.

There was no appreciable change in the blood vessels, nor was there any conspicuous demyelination of the cerebral cortex and white matter. The small nerve cells of the striate body were more severely affected than in Case 1, and there was here a marked proliferation of fibre-producing astrocytes. The globus pallidus and all other diencephalic, mesencephalic, and lower centres were normal.

His third case (Jacob B.) was a man of 54 who had suffered five years previously from pains in the arms and legs and some subjective sense of weakness. At the age of 54 he developed a sensory loss in the left hand, athetosis of the left upper limb and hypertonicity of both upper and lower limbs, particularly on the left side. The deep reflexes were increased, particularly on the left. There was no visual disturbance. He became rapidly demented during the last few months of his illness, developed epileptic convulsions, and died six years after the onset of his symptoms from terminal septicaemia following a crop of boils.

Necropsy showed brown atrophy of the heart, early sclerosis of the aorta, and brown atrophy of the liver. The brain weighed 1,270 g. There was no arteriosclerosis of the large basal arteries, and no macroscopic abnormalities of the brain itself.

The histological changes were very similar to those of Case 2 except that they included the whole of the cerebral cortex, as well as the calcarine region, and a finely meshed status spongiosus was much more frequently found in all cortical regions. Again the internal granular layer was most severely affected, but nerve cell changes, astrocytic proliferation, and status spongiosus were found in all layers, obscuring the cytoarchitecture.

The nerve cell changes were similar to those described in the first two cases, but swelling resembling to some extent primary irritation was more frequent. In the deeper layers of the cortex, and in the subcortical white matter, gemistocytic astrocytes were frequently found. Demyelination was surprisingly inconspicuous and confined to the areas of spongiose degeneration. The blood vessels were normal ; there was no appreciable inflammation, and no senile plaques or neurofibrillary tangles. In the striate body the small nerve cells were chiefly affected but the large nerve cells occasionally showed changes reminiscent of retrograde degeneration.

These three cases have been regarded by Heidenhain and many other subsequent writers as closely related to the Creutzfeld-Jakob syndrome. However, no similar changes have since been reported in the literature, although the number of published cases of the Creutzfeld-Jakob syndrome now totals 31. For this reason the following case, one of seven examples of the Creutzfeld-Jakob syndrome investigated in this laboratory, appears to warrant publication.

Case Report

G. H., a married man aged 38, was admitted to St. Ebba's Hospital on January 29, 1949. About October, 1948, he became forgetful, experienced difficulty in concentrating, and found he could not cope with his work. He became irritable, suffered from headaches, and his vision began to fail. There was no family history of nervous or mental disorder. The patient was stable, married, with two children, and had worked for 20 years at the General Post Office as a sorter. There was no history of previous illness, except that he had sustained severe burns of the legs following the explosion of an incendiary bomb during the war.

On examination he was confused, disorientated, and suffering from a memory defect. There was no abnormality in the cranial nerves. All tendon reflexes were exaggerated but the plantar responses were flexor. A radiograph of the skull was normal. The cerebrospinal fluid showed normal pressure, cytology, and chemistry. The Wassermann reaction was negative in both blood and C.S.F. and the blood urea was 44 mg. per. 100 ml. In February, 1949, it was noted that the discs were pale but not atrophic, and that the tendon reflexes were increased on the left side. There was a " gross ataxia ". He was extremely difficult to examine owing to a rapidly developing dementia, but it was thought that he might have a right homonymous hemianopia. His condition deteriorated rapidly and he died six months after the onset of symptoms.

Necropsy.—A necropsy was performed 24 hours after death. The body was that of an emaciated man with a bed sore over the right buttock. There was no evidence of disease in any system other than the nervous system. The brain weighed 1,200 g. The meninges were normal in appearance as were the blood vessels of the brain. There was a conspicuous widening of the sulci over the convexity of both frontal lobes. Atrophy of the convolutions was also seen posteriorly in the post-central gyrus, dorsal parietal lobule and most marked in both occipital lobes, particularly in the calcarine region. No other macroscopic abnormality was detected.

Histological investigation of the brain showed that the changes were predominantly cortical. All cortical regions were affected, but the most severe change was seen bilaterally in the occipital lobes, particularly in the calcarine regions and their vicinity. Here the convolutions were much reduced in size (Fig. 1). The texture was loosened giving rise in many places to a finely meshed status spongiosus situated particularly, but not exclusively, in the upper layers (Fig. 2). This spongy state appeared to be derived from enlarged perivascular and pericellular spaces. In both the spongiose tissue and the areas of more solid atrophy the cytoarchitecture was grossly disturbed. Most nerve cells had disappeared, the remaining ones showing severe shrinkage and—with fat stains—pigment atrophy. There was an enormous

FIG. 1.—Occipital lobe, Nissl stain, showing atrophy particularly marked on the mesial side, including the calcarine region. × 2·4.

proliferation of microglia, oligodendroglia, and astrocytes, many of the latter of the gemistocytic type (Fig. 3). Compound granular corpuscles were only rarely encountered. The neuroglial proliferation was well demonstrated with Holzer and Hortega's silver carbonate stains (Figs. 4 and 5).

In view of the severity of the lesion in the occipital lobe it is surprising that the stripe of Gennari in the calcarine region was still recognizable in myelin preparations, although staining somewhat paler than is usual. There was considerable demyelination in the occipital cortex, corresponding in severity to that of the other changes. In those parts most severely affected most of the radial and horizontal fibres had either completely disappeared or only remained as fragments. A similar degree of damage to the axis cylinders was noticed in Bielschowsky preparations. With the Herxheimer method fine, brilliantly staining granules would be seen in the remaining nerve cells, microglial and adventitial histocytes, but the amount was not very large and it must be assumed that most of the lipoidal break-down products had been already removed. There was only slight demyelination in the occipital white matter.

The lesions in other areas of the cerebral cortex were less severe. They were of similar degree in the frontal, central (Fig. 6), and temporal convolutions. In Nissl-stained sections the architecture appeared disordered. With higher magnification a diffuse reduction of nerve cells of moderate degree was noticed together with a proliferation of astrocytes and of microglial cells. The Betz cells were not greatly reduced in number, but they appeared shrunken and often contained an excess of lipofuscin. The proliferation of the fibrous glia was, however, moderate in comparison with that seen and illustrated in the occipital lobe. Heidenhain and Bielschowsky preparations revealed a general reduction of fibres in the cortex, but of far less severity than that encountered in the occipital region.

Senile plaques and Alzheimer's neurofibril change were not found. Inflammatory changes were absent, and the iron reaction was negative.

In van Gieson-stained sections the blood vessels throughout showed an adventitial fibrosis, but nowhere was there an appreciable degeneration of the endothelial layer, the internal elastic lamina, or the muscular coat.

No significant change was found in the cerebral white matter except for a slight demyelination in the occipital lobe (mentioned above) and frequent distension of perivascular spaces with terminal oedema around fibrosed blood vessels. The basal ganglia, the brain-

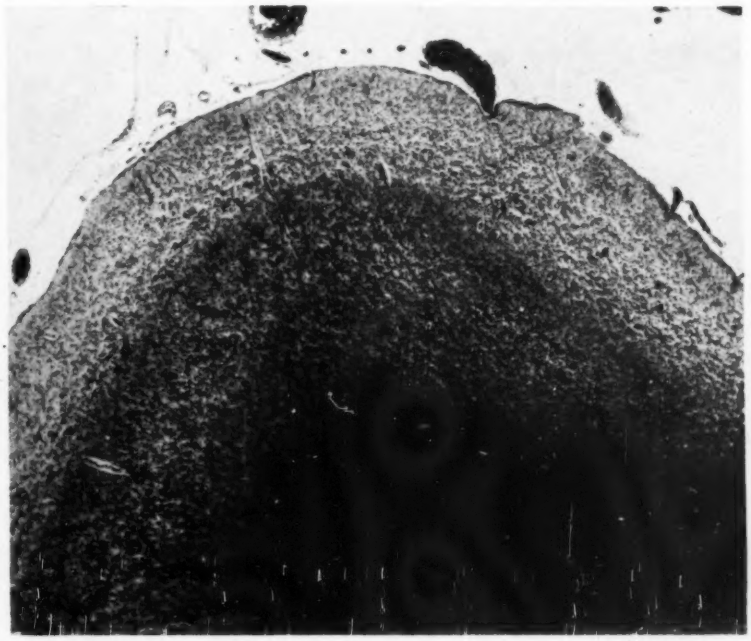

FIG. 2.—Occipital lobe, P.A.H. stain, showing finely meshed status spongiosus particularly in the upper layers. × 26.

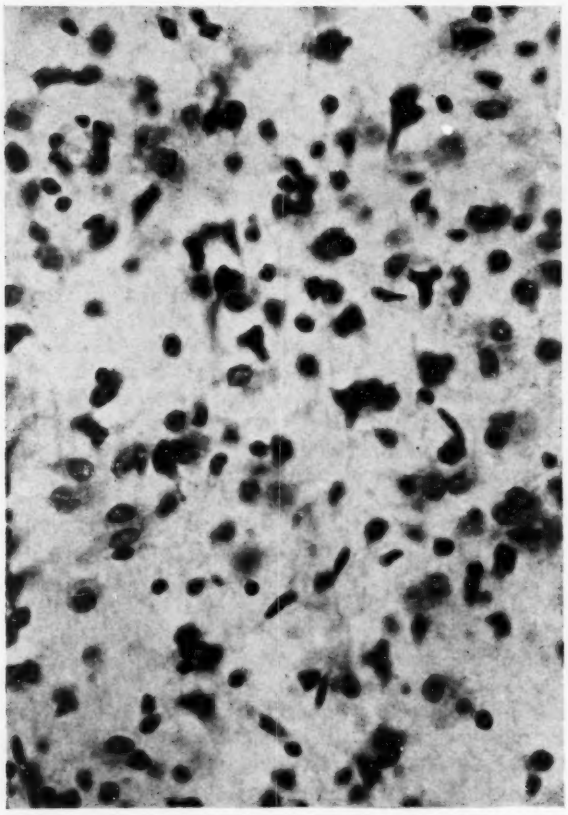

FIG. 3.—Occipital lobe (calcarine region), Nissl stain. Note almost complete disturbance of architecture, severe loss of nerve cells, shrinkage of remaining nerve cells, heavy macroglial (partly gemistocytic) and microglial proliferation. × 500.

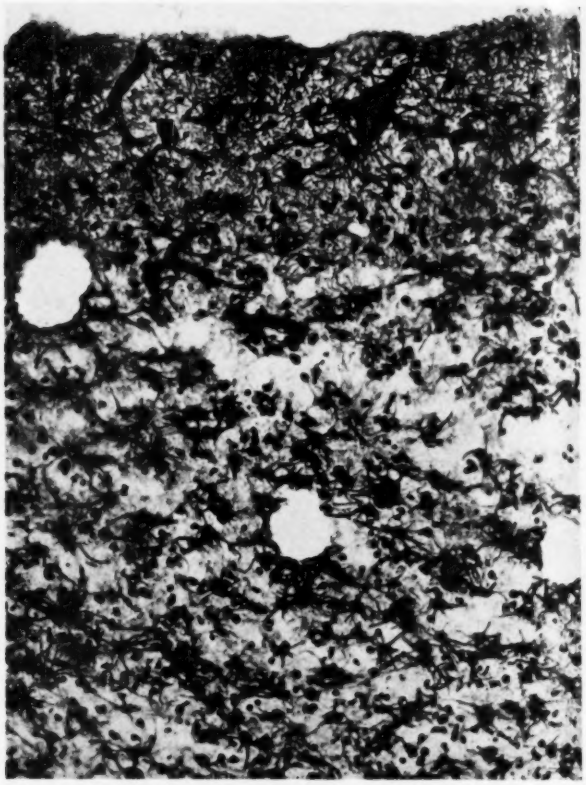

FIG. 5.—Occipital lobe (calcarine region), silver carbonate stain for astrocytes: heavy astrocytic proliferation throughout the upper layers of the cortex. There was less heavy astrocytic proliferation in the deeper layers. × 150.

FIG. 4.—Occipital lobe, calcarine region, Holzer stain. Note the holes of the spongiose state surrounded by glial fibres. × 390.

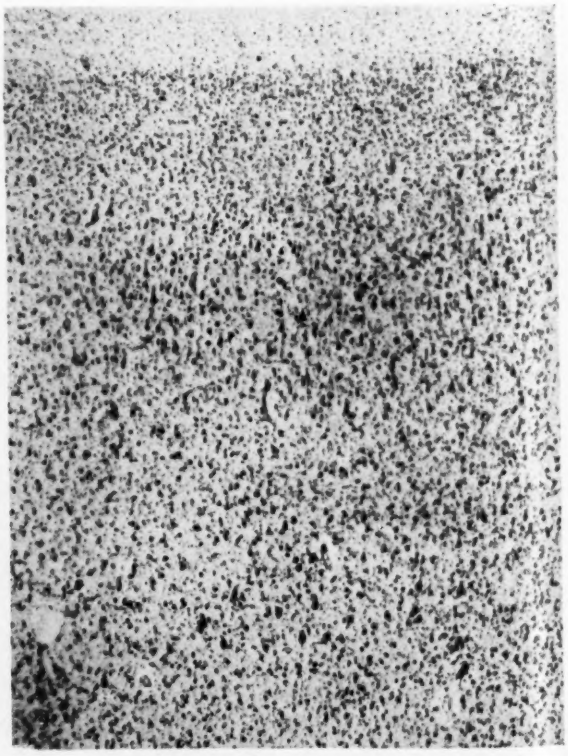

FIG. 6.—Precentral region, Nissl stain, showing disturbance of cyto-architecture through loss of nerve cells in the upper layers and glial proliferation. The Betz cells are shrunken. × 35.

stem, cerebellum, and spinal cord did not show appreciable pathological change.

Discussion

The similarity of our case to Heidenhain's three patients, particularly his patients Eckert and Bleder, needs no further emphasis, for in all three (Eckert, Bleder, our case) a rapidly fatal illness was characterized by blindness and progressive dementia. Although minor differences were present, for instance the absence of athetotic movements in our patient, and the absence of a status spongiosus in the case of Eckert, nevertheless, the general pattern is strikingly similar. In Heidenhain's third case (Jacob B.) the clinical course was much longer and the emphasis on the occipital lobe was less, and did not result in a cortical blindness.

As regards differential diagnosis, gross vascular disease such as arteriosclerosis, aneurysm, or atrophy due to thrombosis of the posterior cerebral artery, could be excluded both in Heidenhain's cases and in our own. Alzheimer's presenile disease is excluded by the absence of senile plaques and of neurofibrillary tangles. The diagnosis of Pick's lobar atrophy is controverted, apart from differences of histological detail, by the localization of the atrophy in the occipital lobes which has never been described in this disease (von Bagh, 1941 ; Peters, 1951). Lissauer's form of general paresis and hepato-lenticular degeneration, in both of which a status spongiosus is found, were excluded by the absence of the characteristic inflammatory change in the one, and of Alzheimer's glial cells in the other.

As has been mentioned, Heidenhain considered his cases to be closely related to the Creutzfeld-Jakob syndrome and this view has been accepted by most subsequent writers. It is not our wish to discuss here the aetiological problems of the Creutzfeld-Jakob syndrome ; this will be done when our material is published in full. Generally speaking the aetiology is still obscure despite the various suggestions which have been put forward. It is even questionable whether the syndrome is more than a convenient dumping ground for otherwise unclassifiable dementias with interesting cross relations to certain systemic degenerations (McMenemey, 1941). If this is the case, the syndrome will sooner or later be reshaped. However, a satisfactory regrouping can only be based upon a larger number of cases than is at present available. It is possible at this stage to distinguish several sub-groups from the point of view of clinical diagnosis. There is first a group with a tendency for degeneration to occur in certain motor centres, at cortical, sub-cortical, bulbar, and spinal levels, clinically presenting as a combination of dementia and amyotrophy, with or without the admixture of extra-pyramidal symptoms. These are the cases for which Wilson (1940) has suggested the term cortico-striato-spinal degeneration. Cases with this symptomatology represent about one-third of the total published material, as well as of our personal material.

The remainder of the published cases of the Creutzfeld-Jakob syndrome consist of conditions in which widespread involvement of the cerebral cortex, often combined with lesions of the basal ganglia, lead to clinical manifestations of which dementia, and pyramidal and extra-pyramidal signs predominate. In most of these cases a clinical diagnosis during life will prove to be impossible since other presenile conditions cannot be satisfactorily excluded.

The group formed by Heidenhain's Cases 1 and 2 and our present case, however, is an exception. With their rapid clinical course, the emphasis of the cortical changes on the occipital lobe, instead of in the motor cortex and with no prominent affection of the basal ganglia, they form a rather distinct group, progressive dementia and blindness being the presenting clinical signs. The rarity of this condition will most likely preclude an accurate clinical diagnosis.

Summary

A case is described which was characterized clinically by a rapid course, cortical blindness, and dementia. Pathologically there was a diffuse cortical degeneration with particular emphasis on the occipital cortex, in which there was a spongiose state.

The condition closely resembles that previously described by Heidenhain, which has been classified as belonging to the Creutzfeld-Jakob syndrome.

In order to distinguish Heidenhain's and our cases from other varieties of the Creutzfeld-Jakob group, the name "Heidenhain's syndrome" is suggested.

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TWO CASES OF CONGENITAL ATRESIA OF THE FORAMINA OF MAGENDIE AND LUSCHKA

BY

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Obstruction of the foramina in the roof of the fourth ventricle is a well recognized cause of hydrocephalus and is usually due to inflammation of the meninges at the base of the brain. In cases of meningitis the foramina may be blocked in the acute stage by exudate, or, in later stages, if resolution is incomplete, by fibrous granulation tissue. In a few cases a history of preceding meningitis cannot be obtained, and at necropsy the meninges at the base of the brain show little or no evidence of preceding inflammation. The foramina cannot be demonstrated and the entire ventricular system is dilated and the lateral recesses ballooned. It has been suggested that such cases either result from a developmental anomaly at the hind end of the ventricle or that there has been a mild, low-grade meningitis unaccompanied by neurological symptoms. In only a few, where examination has included histological study, can the claim for a developmental abnormality be sustained.

Russell (1949) recorded the case of a baby girl aged 1 year in whom hydrocephalus resulted from the presence of a neuroglial septum, incompletely lined by ependyma, which occluded the hind end of the fourth ventricle. She also drew attention to Hilton's case, probably the earliest to be described (Hilton, 1887), in which the foramen of Magendie was occluded by a membrane.

Taggart and Walker (1942) described three cases in which they believed that the hydrocephalus was due to atresia of the foramina of Magendie and Luschka. The striking features of their cases were (1) cystic dilatation of the ventricle which almost filled the entire posterior fossa, (2) malformation of the vermis which was quite small—apparently representing only the anterior vermis—and was displaced upwards by and incorporated in the wall of the cystic ventricle, (3) the high position of the tentorium and lateral venous sinuses. No trace of the posterior vermis was seen nor were the foramina of Magendie and Luschka patent. These authors stated that this condition had been rarely described and apart from two doubtful cases at the end of the last century they were able to find reference to only six cases in more recent times, namely those of Dandy and Blackfan (1914), Pines and Surabaschwili (1932), Castrillón (1933), Scarff (1933), Sahs (1941), and Cohen (1942). Not all of the authors, however, were prepared to accept, or indeed even considered, the theory that both the anomaly of the vermis and the cystic dilatation of the ventricle were secondary to atresia of the foramina. Thus Pines and Surabaschwili (1932), Castrillón (1933), and Sahs (1941) all described their cases as primary aplasia of the cerebellar vermis.

The purpose of this paper is to describe two patients with this unusual condition, who were treated by Mr. W. R. Henderson in the Department of Neurosurgery, The General Infirmary at Leeds, one of whom is still alive, and to draw attention to five further cases described in the recent literature by Shryock and Alexander (1943, one case), Walker (1944, one case), Sidenberg, Kessler, and Wolpaw (1946, one case), and Coleman and Troland (1948, two cases).

Case Reports

Case 1.—The patient was a girl aged 6 years, who until 14 months before had been in good health and had developed normally. She then started to complain of vomiting, especially first thing in the morning. For five weeks before admission she had suffered from increasingly severe headaches. She was admitted to the Neurosurgical Unit on August 29, 1951.

The head was moderately enlarged; there was a cracked-pot note, bilateral papilloedema, and paresis of the right external rectus muscle. There was also slight ataxia of the left arm and the left leg.

The cerebrospinal fluid was normal.

Ventriculography.—The lateral and third ventricles were grossly enlarged and a large collection of air was seen in the posterior fossa (Fig. 1). The line of attachment of the tentorium to the side wall of the posterior fossa

FIG. 1.—Case 1 : ventriculogram showing dilatation of lateral and third ventricles and a large collection of air in the posterior fossa. The tentorium is elevated.

appeared unusually elevated and, moreover, the initial burr-holes, made for ventriculography in what was thought to be the usual position, had exposed the lateral sinus on either side, indicating that the sinuses were higher than normal.

Operation.—The posterior fossa was explored. It was noted that the left side of the posterior fossa bulged rather more than the right and it was only when the bone was removed that it became apparent that the median structures were 2 cm. to the right of the midline. Beneath the dura a large cyst was found lined by a delicate membrane resembling arachnoid. The cyst was in direct communication with and formed part of a greatly enlarged fourth ventricle. The cerebellar hemispheres were 2 cm. apart and between them high up in front a flattened band of tissue, thought to be vermis, was seen. Nothing further was done.

The child died 12 hours after operation.

Necropsy.—The only abnormalities noted were in the head.

The asymmetry of the posterior fossa noted at operation and necropsy corresponded to the asymmetrical expansion of the fourth ventricle. The lateral sinuses and the attachment of the tentorium to the side wall of the posterior fossa were abnormally high.

The ventricle, which resembled a very large cyst, was enormously dilated. A large part of the cyst wall had been removed at operation and only small fragments remained along the line of its attachment to the dorsum of the cerebellar hemispheres, anterior vermis, and dorsal aspect of the upper end of the medulla (Fig. 2).

No trace of the posterior vermis was seen. The anterior vermis was rudimentary and had been displaced upwards and slightly to the right of the midline, so that it lay horizontally. It was difficult to identify the individual lobules, but the vermis probably comprised the lingula, central lobe, culmen, and part of the declive.

The cerebellum had been displaced slightly to the right, and the left hemisphere lay at a higher level than the right elevating the tentorium into the cleft between the ventromedial surfaces of the occipital lobes. The hemispheres were slightly smaller than normal and had been displaced laterally, upwards, and forwards by the expanded ventricle. The maximum diameter of each was 5 cm. The pattern of the cerebellar folia appeared normal and the arachnoid was not thickened.

As a result of these abnormalities the whole of the expanded ventricle from obex below to aqueduct above was exposed to view. Its lateral walls were formed by the medial surfaces of the separated cerebellar hemispheres.

The cyst wall was quite thin and semi-transparent. In the midline rostrally it was attached to the posterior extremity of the rudimentary vermis ; from here the line of reflection extended on either side obliquely in a lateral and posterior direction to reach the extreme lateral aspect of the cerebellar hemisphere near its caudal tip. On the left side it then passed round the lateral border of the hemisphere in an anterior and rostral direction closely following the line of the horizontal fissure till it reached the left lateral recess. Here the membrane had disappeared, but it was seen again attached to the margin of the left restiform body, passing dorsally and medially round the upper end of the medulla towards the obex. On the right side the line of attachment passed from the caudal tip of the cerebellar hemisphere inferiorly along the posterior margin of its medial surface, then anteriorly and rostrally along its inferior margin to the right lateral recess. It then ran posteriorly around the upper end of the medulla to become continuous with the line of attachment already followed to the obex on the left side.

At its line of attachment the membrane was composed

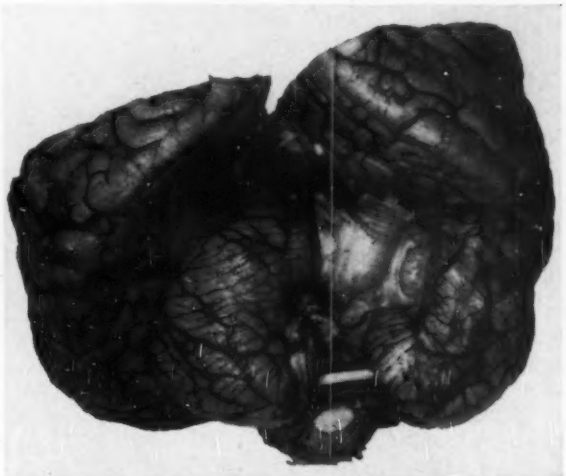

FIG. 2.—Case 1 : cerebellum viewed from below and behind. The cyst wall has been almost entirely removed to expose the dilated fourth ventricle and the rudimentary anterior vermis displaced upwards and to the right.

of two layers, an inner reflected rostrally on to the under surface of the vermis, caudally on to the floor of the ventricle, and laterally on to the medial surface of the cerebellar hemispheres, eventually becoming continuous with the ependyma lining the ventricle itself. The outer layer was reflected rostrally on to the upper surface of the vermis, caudally on to the medulla and laterally on to the lateral surface of the cerebellar hemispheres. These layers are too thin and transparent to be seen in the photograph (Fig. 2). Too much of the cyst wall had already been removed to enable the position of the foramina of Magendie and Luschka to be identified, and the cisterna magna was not seen.

The lateral and third ventricles were markedly dilated. The leptomeninges were healthy.

Microscopy.—The double membrane of the cyst wall (Fig. 3) is composed externally of a layer of vascular collagenous fibrous tissue and internally of a thin layer of neuroglial tissue incompletely lined on its inner aspect by a single row of ependymal cells, columnar in some places, flattened in others. At the site of attachment of the membrane to the cerebellar hemispheres, these two layers are reflected in opposite directions, the neuroglial layer passing medially towards the floor of the ventricle, the fibrous layer becoming continuous with the arachnoid on the lateral aspect of the hemispheres (Fig. 4). The pia formed no part of the cyst wall.

Case 2.—The patient was a girl aged 13 years who was well until three weeks before admission, when she began to complain of increasingly severe headache, later accompanied by vomiting and periodic drowsiness. She was admitted to the Neurosurgical Unit on November 12, 1948.

FIG. 3.—Case 1 : section of cyst wall, showing neuroglial layer lined by ependyma on one side and vascular fibrous tissue on the other (haematoxylin and eosin. × 190).

FIG. 4.—Case 1 : attachment of the double-layered cyst wall to the cerebellum. Note reflexion of the slightly thicker neural layer in one direction and the delicate arachnoidal layer in the other. (Haematoxylin and eosin. × 90.)

There was bilateral papilloedema, bilateral complete sixth-nerve paralysis, and the right plantar reflex was extensor. There was no ataxia. The head was obviously slightly enlarged. The cerebrospinal fluid was normal.

Ventriculography.—The ventricles (Fig. 5) were dilated and there was a large collection of air in the posterior fossa outlining the cerebellar hemispheres below and what appeared to be vermis above. The burr-holes were almost directly over the lateral sinuses, indicating that the latter and the tentorial attachment were in an unusually high position.

Operation.—The posterior fossa was explored and a large, cyst-like structure containing clear fluid and air was encountered beneath the dura. It was formed by a delicate membrane bridging the gap between the cerebellar hemispheres and was apparently an expanded fourth ventricle. When the membrane was incised the cerebellar hemispheres were easily displaced laterally and the whole of the ventricle was brought into view because the vermis was deficient and was compressed upwards and forwards almost to the tentorial opening.

A portion of the cyst was removed and a small window cut in the tentorium.

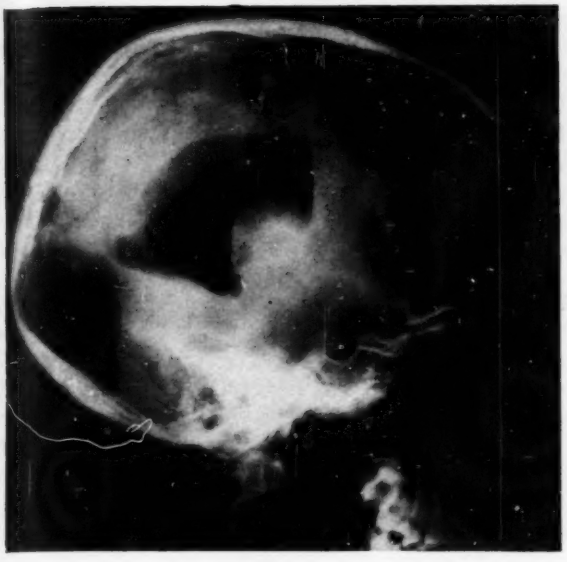

FIG. 5.—Case 2: ventriculogram showing hydrocephalus and a large collection of air in the posterior fossa. The tentorium is raised.

FIG. 6.—Case 2: portion of the cyst wall removed at operation. Note distinct collagenous and neuroglial layers; the latter is lined by ependymal cells. (Haematoxylin and eosin. × 190.)

The child made an uninterrupted recovery and is alive and well four years later. There are no abnormal neurological signs.

Microscopy.—The cyst wall (Fig. 6) removed at operation was similar in appearance to that found in the first case, being composed of a double layer of collagenous and neuroglial tissue.

The second case is apparently similar to the first. Both children presented with signs of raised intracranial pressure, namely, headache, vomiting, and papilloedema without localizing signs, although in Case 1 there was slight ataxia of the left arm and leg. In Case 1 the symptoms were progressive over a period of 14 months, in Case 2 they were present for only three weeks. In both cases the previous medical history was uneventful. Birth and development were normal and there was no history of meningitis. The head of each child was slightly enlarged, but this appears to have escaped notice until admission to hospital. A pre-operative diagnosis was not made in either case, but in retrospect the appearances on ventriculography are believed to be characteristic of this condition in its fully established form, namely, (1) dilatation of the entire ventricular system, (2) a large collection of air in the posterior fossa, (3) a high position of the tentorium and lateral sinuses, which may be observed when the burr-holes are made. Similar *x*-ray observations were made by Taggart and Walker (1942). At operation a large, thin-walled, membranous cyst, filling the posterior fossa, and a rudimentary vermis were found in each case.

Discussion

The cyst may at first be mistaken for a distended cisterna magna, but this idea is readily corrected by further examination, for not only is the cyst found to form part of a dilated ventricle, but histologically it is lined by neuroglia and ependyma on its inner surface. Moreover, in a few cases a normal cisterna magna has been identified below the cyst (Dandy, 1921; Taggart and Walker, 1942).

When the cyst has been correctly recognized as a dilated ventricle, some authors (Pines and Surabaschwili, 1932; Castrillón, 1933; Sahs, 1941, Sidenberg and others, 1946) have considered that the primary abnormality is congenital aplasia of the cerebellar vermis and that the cystic dilatation of the ventricle is secondary, while others (Dandy and Blackfan, 1914; Taggart and Walker, 1942; Walker, 1944; Coleman, and Troland, 1948) have recognized that the enlargement of the ventricle is dependent upon occlusion of the foramina in its roof, and that the anomaly of the vermis is secondary.

The aplasia of the vermis indicates that the condition must arise early in intra-uterine life. If

the primary anomaly affected the vermis it would be difficult to explain the cystic dilatation of the ventricle and the occlusion of the foramina, which do not occur with primary aplasia of the cerebellar vermis. The alternative view that absence or delayed opening or early occlusion *in utero* will be followed not only by hydrocephalus but by failure of the vermis to develop in a normal manner is supported by embryological concepts. This line of reasoning has been adequately dealt with in the paper by Taggart and Walker (1942), in which reference will be found to Weed's experiments on the development of the fourth ventricle and subarachnoid space in the pig, and to the observations of others in the human embryo.

Enlargement of the contents of the posterior fossa *in utero* may also produce secondary changes in the skull and position of the transverse sinuses which are of diagnostic importance to the surgeon. In the normal developing embryo there is a gradual posterior migration of the transverse venous sinuses to their adult position on the occipital bone and postero-inferior angle of the parietal bone which is attained at birth (Streeter, 1915). Dilatation of the fourth ventricle at an early stage may prevent this and the sinuses may remain higher up on the inferior part of the parietal bone where their imprint can sometimes be seen on radiography.

It might be expected that this condition would cause manifest symptoms in infancy and death in early life, but study of the reported cases shows that this is not so. The age at death has ranged from a few months (Russell, 1949; Dandy and Blackfan, 1914) to almost 60 years (Castrillón, 1933) though the majority have been observed during the first two decades. Some have apparently developed normally or had only slight periodical symptoms of raised intracranial pressure, sometimes associated with an enlarging head, before the onset of the final illness, while others have obviously been abnormal from or soon after birth. Why the onset of symptoms should be delayed is not immediately apparent, but the following explanations have been offered :— (*a*) The cyst may act as a semipermeable membrane and allow the passage of some cerebrospinal fluid from the ventricle into the subarachnoid space. (*b*) It has been observed in some cases that the choroid plexus of the fourth ventricle is unusually small and therefore the quantity of cerebrospinal fluid produced may be less. (*c*) The atresia may not be absolute and some cerebrospinal fluid may escape through greatly narrowed foramina.

There is nothing in the clinical history of these patients to suggest the nature of the underlying condition responsible for the hydrocephalus. If the abnormally high position of the transverse sinuses is recognized radiographically, then the condition should be suspected. In the typical case the ventriculographic appearances are characteristic. It is of interest to note, that in neither of the cases described by Coleman and Troland (1948) were these radiological appearances present, and the authors suggested that this was probably due to early equilibrium allowing normal migration of the sinuses.

The operative mortality is unfortunately high, though the technical procedure of removing part of the cyst membrane and allowing free communication between the fourth ventricle and the subarachnoid space is relatively simple and has proved effective in some cases. Successful results have been recorded by Scarff (1933), Cohen (1942), Walker (1944), and Coleman and Troland (1948) (two cases), in addition to the second case reported here.

Summary

Two cases are described of an anomaly of the cerebellar vermis associated with cystic dilatation of the fourth ventricle and hydrocephalus.

Reference is made to similar cases reported in the literature and reasons are given for the belief that the condition is due to partial or complete failure of the foramina of Magendie and Luschka to become patent at or about the fourth month of intra-uterine life.

The clinical and radiographic features are discussed. The appearances on ventriculography are considered to be diagnostic of the condition.

One patient is alive and well four years after operation, the other died shortly afterwards.

I wish to thank Mr. W. R. Henderson and Professor R. A. Willis for their encouragement and advice during the preparation of this paper, Mr. W. H. Lawson for technical assistance, and the Department of Medical Photography, University of Leeds, for the photographs. Case 1 was referred to the Department of Neurosurgery by Dr. E. C. Allibone and Case 2 by Dr. J. A. Price.

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AUTONOMIC CHANGES AFTER UNILATERAL LEUCOTOMY

BY

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Kennard (1944) has reviewed both the clinical and experimental evidence of "cortico-autonomic" interrelations. At that time she suggested that the frontal poles were autonomic centres distinct from the motor cortex but was able to adduce little evidence as to their exact role. Since Kennard's review Reitman (1945) and several subsequent authors have reported transient changes in autonomic regulatory functions following prefrontal leucotomy. Apart from the observations of Fairman and his co-workers (Fairman, Livingston, and Poppen, 1950), we are not aware of any previous studies to investigate whether unilateral autonomic changes can be demonstrated following unilateral leucotomy. In the present paper we report a series of such studies in which bilateral recordings of skin temperature and skin resistance have been made before and after unilateral operations on the frontal lobes. Differences in skin temperature between the two upper limbs were sought, both in the resting condition and after heating and cooling. Measurements of palmar skin resistance, an established method of studying sudomotor activity (McCleary, 1950), were made in the resting state, and the fall in skin resistance (psycho-galvanic response) following various stimuli recorded. Unilateral leucotomy was not in favour for long and our observations are confined to four cases.

Methods

In the absence of a constant temperature room, recordings were made at the temperature prevailing in the laboratory. The subjects sat lightly clad with their arms supported comfortably at heart level. They were shielded from draughts and throughout the examination period their arms were equally exposed. The temperature changes following heating and cooling were measured in the wards with the patients lying flat and shielded from draughts.

Temperature changes were measured with thermocouples and except for those following heating and cooling the readings were obtained from the pulp of the thumbs. Observations of resting skin temperature and skin resistance were made at the beginning and end of each test session, and those reported here were the final values recorded and were made after exposure to the laboratory temperature for at least half an hour.

Skin resistance was measured with an apparatus essentially the same as that described by Grant (1946), a graphic record of galvanometric changes being recorded on moving photographic paper. To obtain simultaneous responses the apparatus was duplicated. In order to ensure that any disparity between responses recorded from the two sides was not an artefact resulting from differences in the recording apparatus the analysis has been confined to observations which were controlled by alternating the two recording systems in a balanced manner with respect to the two hands. Various methods of stimulation were tried with the first two patients studied. We report here results which can be grouped either as responses to shocks or as responses to psychological stimuli. The psychological stimuli included intellectual tasks, impertinent questions, and warning light signals regularly preceding electrical shocks. The other two patients were examined by an identical procedure on each occasion except for the first recording with subject E. S. This procedure was adapted from one we have used to study pain perception before and after standard leucotomy. In the present investigation it consisted of a series of shocks, increasing regularly in strength, which were applied to the fifth fingers of each hand in balanced blocks, i.e., in the series . . . RLLR—LRRL. Each shock was preceded by a warning light and the time between the warning light and the presentation of the shock was 7 seconds. This allowed sufficient time for a psychogalvanic response to occur to the light and to be recorded before the arrival of the shock. This response to the light was not a time-conditioned response: it depended largely on its psychological significance as a warning signal and was greatly reduced or even abolished when the subject was told that no more shocks would follow.

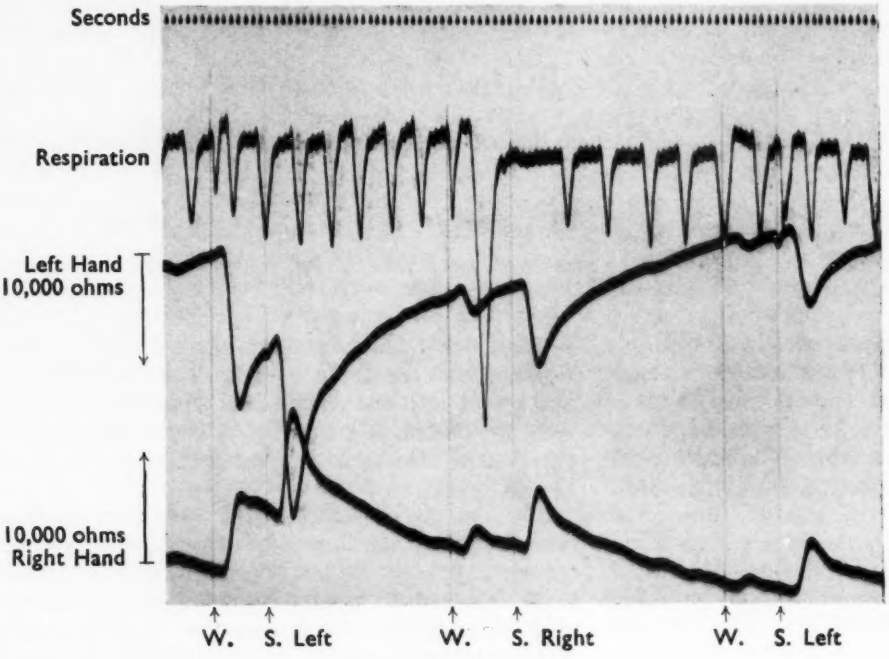

FIG. 1

Fig. 1 is a sample from a typical record. We have shown elsewhere (Elithorn, Piercy, and Crosskey, 1951) that unilateral shocks to the hand can produce an autonomic response which is bigger on the side stimulated than on the contralateral side. It follows that if, owing to differences in tissue resistance, the shocks to one limb were effectively less powerful, then there would be an apparent reduction in the mean response on that side. Inspection of the detailed data has enabled us to exclude this factor as an important one except on one occasion, which is discussed below. The psychogalvanic responses to the warning signal are of course free from bias from the side of the subsequent shocks, and where both types of response were recorded the lateral preponderance is the same for each, except on one occasion. On this occasion the difference between the means for the psychological responses was small and did not satisfy the test for significance. All comparisons of means between the two sides have been tested for their statistical significance. The variability of the psychogalvanic responses, even with apparently equal stimuli, is always large. This variability, however, has been almost excluded and our tests of significance made the more sensitive by using Student's t test for paired observations (Fisher, 1946). Since the variability of the means themselves is irrelevant, their standard deviations have not been included in the table.

Shock stimuli were given from a constant voltage Ediswan square wave stimulator.

Subjects

All four subjects were fully right handed. The clinical history and post-operative course of these subjects will be published elsewhere and only a bare outline is given below.

Case 1.—E. R. (hospital no.13043), a woman aged 63, had severe post-herpetic pain in the left chest (D.8) of 15 months' duration. Medical treatment, deep *x* rays, and section of the dorsal roots D.7 to D.11 produced only transient effects. Left unilateral leucotomy in a coronal plane 3 cm. behind the external angle of the orbit was performed. Following operation there was a very temporary reduction in her affective responses to her pain.

Case 2.—H. W. (hospital no. 17797), a man aged 63, had severe right trigeminal neuritis of 10 years' duration. Medical treatment and alcoholic injections of the Gasserian ganglion on three occasions had failed to produce permanent relief. Full right prefrontal leucotomy carried out in a coronal plane 3 cm. behind the external angular process produced a marked alleviation of his symptoms. This persisted for three months with gradual relapse over the next three months.

Case 3.—E. S. (hospital no. 18957), a woman aged 53, had severe post-herpetic pain in the right side of the chest, D.5–D.6, of two years' duration. She had always suffered from migraine (right hemicrania). A full right leucotomy in a coronal plane was performed. Post-operatively there was a short period of apathy and a reduction in spontaneous complaints of her pain.

Case 4.—L. B. (hospital no. 29566), a woman aged 34, had disseminated sclerosis with pain in the left arm and face, central in type, and of 10 years' duration. Treatment with medicine and, on two occasions, by the alcoholic injection of the trigeminal nerve, had produced no relief. Right prefrontal leucotomy was carried out in a plane anterior to the lateral ventricle and sloping back slightly from the wing of the sphenoid. There was a temporary reduction in the frequency of the attacks of pain and in their subjective intensity.

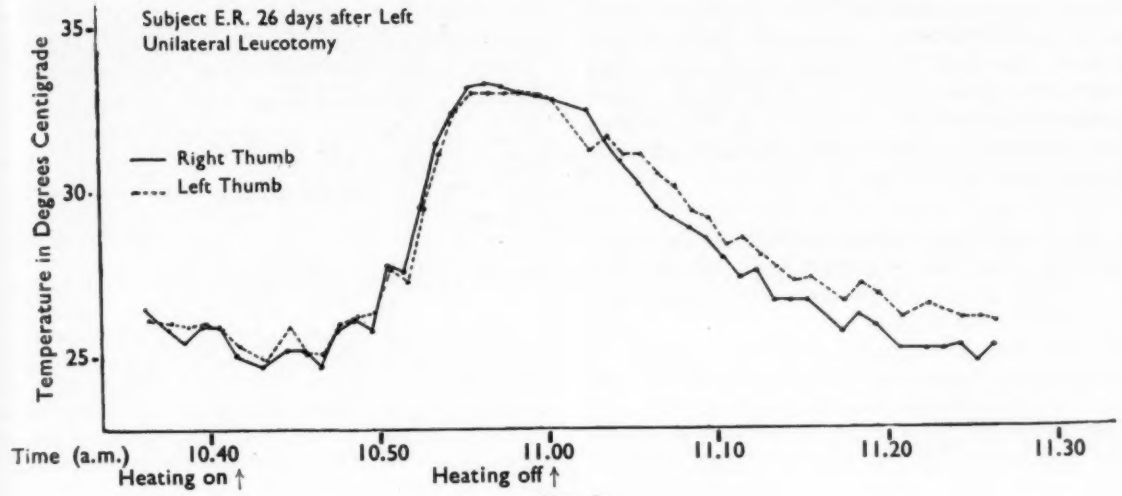

FIG. 2A

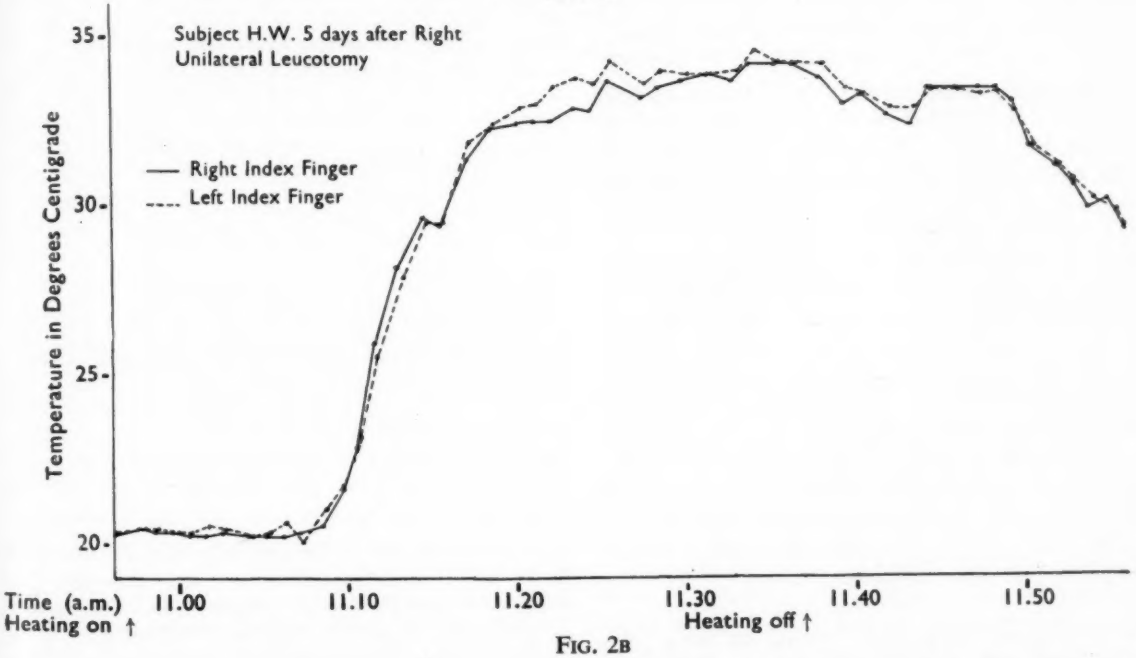

FIG. 2B

Results

Changes in Skin Temperature after Heating and Cooling.—Fig. 2 shows for two subjects the changes in skin temperature which occurred on the two hands when the trunk was heated and subsequently allowed to cool. Fig. 2a is drawn from recordings made with subject E. R. 26 days after a left unilateral leucotomy. It will be seen that the original resting levels in the cold state were identical, that both hands started to warm up at the same time, that the temperature increased at the same rate, and that there was no appreciable difference between the hands when the maximum dilatation was obtained. During the subsequent period of cooling the left thumb showed a slight delay, but the temperature difference is never greater than 1·5° C. Netsky and Starr (1948) state that temperature differences between two normal hands under resting conditions may reach 2° F. In the pre-operative control recording made with this patient the difference between the two hands was as great as 2° F. on at least one occasion. Fig. 2b shows the results of a similar test made with subject H. W. five days after a right unilateral leucotomy. Again the resting levels are identical and heating and cooling proceeds at the same rate.

The pre-operative control figures are not presented since no post-operative differences between the sides were observed. The only point noted was that post-operatively the response to heating and cooling appeared to be brisker: however, as the rates of heating and cooling were quite uncontrolled, this observation has little value.

Resting Skin Temperatures and Skin Resistance.—These showed no consistent differences between the sides. Table I gives the data for resting skin

TABLE I

RESTING SKIN TEMPERATURE IN RELATION TO THE SIDE OF THE LESION

Mean Skin Temperatures (°C.)	Before Unilateral Leucotomy (n = 10)	After Unilateral Leucotomy (n = 19)
Ipsilateral limb ..	31·3 (S.E. = 3·91)	32·9 (S.E. = 2·72)
Contralateral limb..	31·4 (S.E. = 3·56)	32·9 (S.E. = 2·52)

temperatures in a summarized form. It will be seen that there is a slight increase in the values recorded after the operation. The change itself does not reach a significant level of confidence and no attempt has been made to evaluate changes in environmental temperature. It affects each side equally.

Most of the figures for resting skin resistance are included in Table II. Only subject L. B. shows a marked post-operative discrepancy and that on one day only. This discrepancy is supported by the findings with the psychogalvanic responses and will be discussed below. A few additional readings of skin resistance in the resting state were obtained on days other than those on which responses to stimuli were recorded. These contribute little but do show that in subject E. R. the post-operative tendency for levels to be higher on the left was present before operation. They are not presented here.

Psychogalvanic Responses.—Table II gives the mean results obtained at each session with each of the four subjects.

Subject E. R.—Left-sided pain; left prefrontal leucotomy. Pre-operatively this patient was only examined with shocks as the stimulus. On both occasions the responses were larger on the right. Examined on the third post-operative day no change was detected but when re-examined on the seventeenth day the responses to shocks were bigger on the left. This finding exceeded the 5% level of confidence and was confirmed by the responses to psychological stimuli. Seven days later the observations were repeated and, although the number of observations was fewer, when the two types of stimuli were considered together the size of responses on the left

TABLE II

EFFECT OF UNILATERAL LEUCOTOMY ON SKIN RESISTANCE LEVELS AND PSYCHOGALVANIC RESPONSES

No. of Days before and after Operation	Resting Skin Resistance Levels (ohms × 10^3)		Psychogalvanic Responses (mean levels in ohms × 10^3)					
			To Painful Shock			To Psychological Stimuli		
	Left	Right	Left	Right	n	Left	Right	n
Patient E.R. (left-sided pain, left-sided leucotomy)								
−5	—	—	6·4	*7·7**	26	—	—	—
−3	—	—	8·7	*9·2*	16	—	—	—
+3	97	87	7·2	7·9	20	—	—	—
+17	68	66	*7·9**	7·0	18	7·9	6·8	9
+24	91	58	5·5	3·4	8	4·6	3·9	6
+122	97	105	14·1	12·5	10	—	—	—
Patient H.W. (right-sided pain, right-sided leucotomy)								
−7	—	—	—	—	—	*2·3†*	1·2	27
−1	61	67	1·9	2·0	16	0·9	1·0	27
+11	85	109	—	—	—	*2·3**	1·5	17
+14	70	66	1·0	0·8	12	4·8	4·4	5
+194	83	92	3·0	4·7	24	1·6	*2·2†*	55
Patient E.S. (right-sided pain, right-sided leucotomy)								
−10	91	95	—	—	—	*24·1**	19·8	10
−6	106	92	*13·0†*	7·1	16	*8·1‡*	5·3	22
−3	113	114	*12·4‡*	7·8	30	*12·0‡*	8·6	36
+7	180	188	16·2	7·0	30	*9·0‡*	3·7	42
+11	—	—	*5·3†*	2·1	16	1·6	0·8	13
+25	163	160	*29·7†*	15·3	16	*5·0**	1·6	20
+42	105	120	*13·9†*	9·2	20	3·8	2·9	25
+163	120	99	7·9	4·9	16	5·5	3·5	14
+499	140	120	13·8	13·9	24	3·8	4·0	24
Patient L.B. (left-sided pain, right-sided leucotomy)								
−1	138	134	*20·1†*	17·5	24	11·7	12·1	24
+10	92	163	18·4	*36·7‡*	24	1·0	*4·6‡*	32
+14	113	112	21·0	21·5	32	*7·8‡*	6·7	42
+92	136	146	*14·6**	10·0	16	2·5	2·4	33

* Significant at the 5% level.
† Significant at the 1% level.
‡ Significant at the 0·1% level.

Those responses which are significantly greater than those on the opposite side are printed in italics. The actual level of confidence is also given.

significantly exceeded the size of those on the right. When the patient was followed up and examined four months post-operatively the change was still apparent, although not enough observations were made to establish its significance.

Subject H. W.—Right-sided pain; right-sided leucotomy.

This patient showed considerable variation both before and after the operation which, though marked in its clinical results, failed to produce any clear-cut effect on the autonomic responses.

Subject E. S.—Right-sided pain; right-sided leucotomy.

This patient was examined repeatedly both before and after operation. On three occasions pre-operatively it was shown that her responses on the right were between 20% and 30% smaller than those on the left. Following a right-sided prefrontal leucotomy this discrepancy was

markedly exaggerated, the responses on the right being reduced to less than half the corresponding responses on the left. This phase of relative reduction of the responses on the right decreased and, when re-examined 15 months after operation, the responses on the right were bigger than those on the left. Though not in itself significant, the difference between the two sides is in the opposite direction from that found immediately post-operatively and is significantly different from it and from all the pre-operative observations.

Subject L. B.—Left-sided pain ; right-sided prefrontal leucotomy.

Examined 10 days after the operation this patient showed a marked reduction of the responses on the left or contralateral side. This temporary change was accompanied by a corresponding difference between the two limbs in the resting level of the skin resistance. At the beginning of the test session the skin resistance was 167×10^3 ohms on the right and 112×10^3 ohms on the left. Over an hour later, with the right and left limbs equally exposed in a draught-free atmosphere, the figures were 163 and 92 respectively. This marked difference in skin resistance was reflected by a reduced effect of the shock on the right. As explained above, this would be likely to cause an apparent reduction of the responses on the right side. In fact, the responses to the shocks are bigger on the right, although much less so than is the case with responses to psychological stimuli. These responses would, of course, be unaffected by the differences in effective shock strength.

To summarize the results obtained with these four patients : one, H. W., showed no consistent effect. One, E. R., showed a persistent relative decrease in the contralateral limb (R). A similar but transient decrease in the contralateral limb (L) was seen in subject L. B. Subject E. S., however, who received the most detailed study, showed a relative increase in the contralateral limb (L). This persisted for at least a month post-operatively and was then gradually replaced by a relative over-activity of the ipsilateral side.

It is worth noting that each of the four subjects showed on at least one occasion pre-operatively a significant difference between the responses on the two sides. These differences are greater than would be expected from our own unpublished observations of bilateral responses in normal subjects. In each case where there is a significant difference between the responses these are smaller on the side of the body afflicted by pain. Korr (1949) has shown that areas of low skin resistance occur in areas segmentally related to painful lesions. Our figures do not show constant differences in resting skin resistance, but only one patient, L. B., had pain which was segmentally related to the recording electrodes (C.6—C.8). In this case the lesion was thought to be central.

Discussion

Reitman (1945) and many other workers have demonstrated changes in autonomic functions following bilateral prefrontal leucotomy. Taking advantage of this operation Livingston and his co-workers (Livingston, Chapman, Livingston, and Kraintz, 1948) have shown that electrical stimulation of the orbital surface of the frontal lobes may cause marked changes in the blood pressure and in respiration. Unfortunately they were not able to look for different vasomotor responses on the two sides of the body. In a subsequent publication, moreover, Chapman, Livingston, and Livingston (1949) stated that their results might have been due to spread of the excitatory current to the temporal lobe. The majority of earlier experimental work on cortical autonomic control, most of which has been reviewed by Kennard (1944), has indicated that focal changes in vasomotor tone or sudomotor activity are associated with either stimulation of or damage to the sensorimotor cortex. Netsky and Starr (1948) have more recently discussed the literature and reported their own careful observations on 50 cases of focal head injury. They showed that removal of the post-central gyrus for traumatic epilepsy was followed by an increase in sweating on the contralateral side. Of the 50 cases, 22 showed differences between the two sides either in sweating or skin temperature. The lesions in almost all these cases were confined to the region of the sensorimotor cortex. Netsky and Starr conclude that their study indicates that the post-central gyrus is the posterior limit of the area with direct cortical representation of autonomic functions. The anterior limit beyond the pre-central gyrus is, they state, not known. However, nine of these authors' cases had damage which was limited to the frontal lobes. Of these nine cases six showed no lateral differences in autonomic function. One with bilateral damage and with a history of left hemiparesis showed increased sweating on the right and decreased skin temperature on the right. Another case with cortical damage in the inferior part of the left frontal lobe showed a contralateral increase in sweating, but in this patient too there was evidence of involvement of motor areas in that he had had an aphasia. The remaining patient showed decreased sweating on the contralateral side. There was no evidence of any motor or sensory deficit, though it is noted that the trauma involved the anterior longitudinal sinus. Thus of seven patients with lesions wholly anterior to the primary motor cortex only one showed a unilateral disturbance of resting autonomic function. These findings of Netsky and Starr confirm those of Lund (1944) who also studied a series of patients with

unilateral autonomic changes. Lund concluded that the cortical vasomotor centres lay within the motor and premotor areas and also in the parietal lobe. Fairman and his co-workers showed in three cases that following unilateral leucotomy the resting skin temperature in the first post-operative fortnight was less than two degrees lower on the side contralateral to the lesion.

Our own four subjects all had unilateral lesions involving the frontal lobes anterior to the motor areas. None showed any evidence of motor impairment. Although there was no clinically obvious alteration of autonomic function and only on one occasion evidence of changes in autonomic tone in the resting state on the side contralateral to the lesion, analysis showed that in three out of the four patients there was a definite change in the relative responsiveness on the contralateral side. (Two patients, E. R. and L. B., showed in the post-operative period a relative decrease on the contralateral side. The other patient, E. S., showed an increase on the contralateral side.) Guttmann (1931) has maintained, and Netsky and Starr's results also suggest, that lesions of the cortex may in different subjects cause autonomic changes in the contralateral limb which are different in sign. The vast literature on the clinical effects of leucotomy shows that similar operations on the frontal lobes will relieve both (1) conditions characterized by anxiety and with over-activity and excitation of the autonomic system, and (2) conditions marked by profound depression or inhibition of both the intellectual and autonomic life. It is perhaps unreasonable therefore to regard the highest centres of nervous integration as either primarily inhibiting or primarily exciting. In fact there may be no anatomical distinction between mechanisms which reduce activity level and those which increase it. Damage to structures involved in such central mechanisms may cause secondary imbalance in lower centres. These disturbances may well be greater in the injured hemisphere and thus be reflected in a changed responsiveness in the autonomic responses of the contralateral limb.

Summary

Autonomic reflexes have been studied in four patients before and after unilateral leucotomy. The results provided no evidence of the presence of prefrontal cortical autonomic centres for the focal control of vascular or sweating responses. However, changes in responsiveness, different in sign in different subjects, support the suggestion that the frontal lobes exert both inhibitory and excitatory influence on centres which do have focal autonomic functions. Earlier experimental work and clinical observations suggest that such cortical autonomic control is centred around the sensorimotor areas.

Our thanks are due to the members of the hospital staff who allowed us to study their patients and in particular to Dr. E. A. Carmichael, whose encouragement and help made this study possible.

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A COMPARISON OF ISONIAZID WITH MODIFIED INSULIN THERAPY IN NEUROTIC STATES

BY

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A method of insulin treatment directed towards increasing the patient's weight and feeling of physical well-being and reducing feelings of tension and anxiety is commonly employed in the treatment of selected neurotic conditions (Sargant and Craske, 1941; Tomlinson and Ozarin, 1942; Sargant and Slater, 1948). The dosage of insulin and the taking of food are so arranged that actual coma is never reached. This form of treatment has become known as modified insulin therapy. However, a striking increase in appetite and food consumption, with apparent restoration in energy, was also noted by Robitzek and Selikoff (1952) in their investigations on the effect of isonicotinic acid hydrazide (isoniazid) in tuberculous patients, and the possibility therefore arose of being able to employ isoniazid in the physical therapy of neurotic breakdowns. It was considered that, if isoniazid was found to be effective as an alternative to modified insulin therapy, the ease of administration and simple supervision involved in its use might confer upon it practical advantages over insulin. With the latter possibility in mind, an investigation was planned to test the relative merits of isoniazid and insulin in the treatment of neurotic disorders.

Materials and Methods

"Modified Insulin Group".—The patients, who were all males, fasted from 8 p.m. the previous evening. At 7 a.m. the following day they were given an intramuscular injection of 20 units soluble insulin and this was immediately followed by the oral administration of two inert tablets (specially prepared by Messrs. Savory and Moore). These tablets were employed to control the effect of giving isoniazid tablets in the other group of subjects under investigation. At 10 a.m. the patients received a standard breakfast consisting of the following:

20 oz. (weighed out) boiled potatoes.
4 slices bread and margarine.
1 cup of coffee.
Jam (or marmalade) as required.

At 7 p.m. the patients were given two further inert tablets for control purposes. The dose of insulin was increased by 10 units each day until a maximum of 40 units was reached. All the patients remained on the standard hospital diet and they were not allowed to obtain eatables from outside the hospital. In connexion with the latter, it should be stated that, for the patients involved, all parole was cancelled during the investigation and the relatives were not allowed to bring any foodstuffs into the hospital. Each patient underwent treatment daily (with the exception of Sundays) for a period of four weeks.

The investigation was carried out in a special room which was normally utilized for modified insulin therapy and the nurses in charge were experienced in this form of treatment.

"Isoniazid Group".—Two tablets of isoniazid (100 mg. each) were given at 7 a.m. and 7 p.m. respectively in place of the inert tablets included in the "modified insulin group" and, in addition, sterile water was substituted for the soluble insulin administered to the other group of subjects. Apart from these differences, the remaining procedures were identical in each of the two groups.

None of the patients included was informed about the two separate types of treatment employed. Strict secrecy was maintained on this point so that the subjects were quite unaware of the different drugs involved. The absence of any apparent distinction between the two groups was further emphasized by the fact that the words "Insulin Treatment" were printed on the door leading into the room utilized for this study.

The ages of the patients, and the conditions from which they were suffering, are shown in Tables I and II.

It will be seen that only eight patients were included in each of the two groups. The original intention, however, was to study a larger series of subjects, but due to the recorded results and subsequent clinical impressions of how the patients

TABLE I
CASES ON MODIFIED INSULIN THERAPY

Case No.	Admitted	Diagnosis	Age	Therapy Begun	Therapy Ended
1	19. 6.52	Anxiety state	37	10. 7.52	6. 8.52
2	15. 7.52	Hysteria	28	25. 7.52	21. 8.52
3	30. 7.52	Anxiety state	27	13. 8.52	9. 9.52
4	23. 8.52	Anxiety state	35	27. 8.52	23. 9.52
5	2. 9.52	Anxiety state	24	8. 9.52	5.10.52
6	4.11.52	Neurotic depressive reaction	29	11.11.52	8.12.52
7	6.12.52	Neurotic depressive reaction	31	10.12.52	6. 1.53
8	9.12.52	Anxiety state	26	12.12.52	8. 1.53

TABLE II
CASES ON ISONIAZID

Case No.	Admitted	Diagnosis	Age	Therapy Begun	Therapy Ended
1	7. 7.52	Anxiety state	19	11. 7.52	7. 8.52
2	11. 7.52	Neurotic depressive reaction	32	16. 7.52	12. 8.52
3	11. 7.52	Neurotic depressive reaction	32	16. 7.52	12. 8.52
4	13. 8.52	Neurotic depressive reaction	38	14. 8.52	10. 9.52
5	29. 8.52	Neurotic depressive reaction	21	3. 9.52	30. 9.52
6	6.10.52	Anxiety state	34	8.10.52	4.11.52
7	7.10.52	Anxiety state	38	12.10.52	8.11.52
8	30.12.52	Anxiety state	35	12. 1.53	8. 2.53

responded, it was considered unfair to extend the investigation to other subjects.

The changes in body weight and the subjective response to treatment were investigated in each group of patients.

Results

Changes in Body Weight.—Each subject was weighed immediately before beginning treatment (in the early morning) and on the morning following the last day of treatment. The same scales were utilized throughout and the same male nurse weighed each patient. The findings are shown in Tables III and IV.

It will be seen that in the group undergoing modified insulin therapy there was a consistently greater increase in weight than was to be found in the " isoniazid group ". Though the total number of subjects investigated was small, it was considered of interest to apply a statistical test to determine whether or not these increased weight gains were likely to have been due to chance. Since the average initial weights did not differ significantly ($P>0.7$), the difference between the weight gains in the two groups was probably real ($P<0.001$).

TABLE III
CHANGES IN BODY WEIGHT BEFORE AND AFTER MODIFIED INSULIN THERAPY

Case No.	Weight before Treatment (st. lb.)	Weight after Treatment (st. lb.)	Weight Gain (lb.)
1	8 10	9 4	8
2	9 9	10 1	6
3	8 12	9 7	9
4	8 1	8 7	6
5	6 6	7 1	9
6	10 10	11 7	11
7	8 3	9 4	15
8	8 7	9 3	10

TABLE IV
CHANGES IN BODY WEIGHT BEFORE AND AFTER ISONIAZID TREATMENT

Case No.	Weight before Treatment (st. lb.)	Weight after Treatment (st. lb.)	Weight Gain (lb.)
1	9 9	9 12	3
2	8 7	8 11	4
3	8 2	8 4	2
4	9 2	9 6	4
5	10 7	10 7	0
6	7 12	8 2	4
7	8 7	8 6	No gain (Minus 1 lb.)
8	8 12	9 0	2

Subjective Response to Treatment.—On the day following the completion of the course of treatment, each patient was asked, " Do you think the treatment has had any effect on you ? " If the reply to the latter was in the affirmative, the subject was further asked, " What effect has it had ? " The findings are shown in Tables V and VI.

TABLE V
SUBJECTIVE RESPONSE TO TREATMENT (MODIFIED INSULIN)

Case No.	Positive Effect	Nature of Effect
1	Yes	" Sort of built me up. Made me physically fit again. I feel more lively in myself, sort of thing."
2	Yes	" I can eat breakfast now. I couldn't before. I feel definitely fitter, sir."
3	Yes	" I feel a lot stronger and I'm eating more. I've got an appetite for my breakfast now. I feel a lot better in myself. More jovial, like."
4	Yes	" It's made me feel stronger. I can work and I've got more confidence in myself."
5	Yes	" I've got more confidence in myself now. I feel much stronger as well."
6	Yes	" I feel much better. I don't feel so nervous. I feel better in myself."
7	Yes	" It's certainly made me put on weight and I feel more lively. I certainly don't get so depressed as I did."
8	Yes	" It's certainly made me more vigorous."

TABLE VI
SUBJECTIVE RESPONSE TO TREATMENT (ISONIAZID)

Case No.	Positive Effect	Nature of Effect
1	No	Nil applies.
2	Yes	" More invigorated."
3	Yes	" I've never felt so well in my life and I've never felt so happy."
4	Yes	" It's given me a rest."
5	" It's hard to say."	" My legs ache when I lie in bed and I can't sleep."
6	Yes	" Done me the world of good, without telling lies."
7	Yes	" Honestly speaking, it made a big change inside me. It stopped the panics I had."
8	Yes	" I feel a different man altogether. I've regained my confidence and I feel my normal self."

Table V shows that almost all the patients on modified insulin therapy considered that the treatment had increased their appetite and enabled them to put on weight. In fact, patient No. 6 was the only subject in this group who did not explicitly state that the treatment had had a beneficial effect on his physical condition. In the group treated with isoniazid, however, the replies to questioning were of a much more nebulous character. In this latter group, no subject, apart, perhaps, from patient No. 2, made any obvious reference to the effect of the treatment on his physical well-being, and two of the subjects (Nos. 1 and 5) did not consider that the treatment was of any positive value whatsoever.

It should be stated that, in addition to the recorded observations on body weight and the subjects' own impressions of the effect of treatment, there was general agreement between the nurses in charge of the patients and myself on the fact that the clinical progress—both physical and psychological—of the patients treated by modified insulin therapy appeared to be consistently superior to that of the patients treated with isoniazid. It was for this reason that the investigation was not extended to a larger series of subjects.

Discussion

Robitzek and Selikoff (1952), in their investigations of the effect of isonicotinic acid hydrazide on patients suffering from "hopeless" pulmonary tuberculosis, noticed "a sharp return in sense of well-being", markedly increased appetite, rapid weight gain, and restoration of energy. These beneficial effects have not been reproduced in the present study of neurotic patients in whom overt evidence of tuberculosis was not present. It is true that most of the subjects in the "isoniazid group" stated that they felt greatly improved following treatment but it seems probable that this was largely due to the suggestive effect of the régime. In the words of Robitzek and Selikoff (1952), "... it is a matter of major perception to eliminate the psychologic aspects inherent in a group entirely aware that it is receiving special attention." The fact remains that, though both groups of subjects were taking part in a superficially similar programme of treatment, the increase in weight of the patients undergoing modified insulin therapy was significantly greater than that of the "isoniazid group" and this observation was supported by the subjective response of the patients to treatment.

It would seem that the increase in weight and general physical well-being consequent upon the use of isoniazid in pulmonary tuberculosis is directly due to the effect of therapy on the actual tuberculous process. Alternatively, work on the "animal protein factor" (e.g., Cunha, Burnside, Buschman, Glasscock, Pearson, and Shealy, 1949; Biely and March, 1951) suggests the possibility that isoniazid may produce some of its effects by virtue of being an animal protein factor. This mode of action receives support from Barnard, Orens, and Schwartz (1952), who state that isoniazid may induce a rapid gain in flesh in many non-tuberculous conditions. (They suggest, on the basis of their views on the mechanisms involved, that the designation "A.P.F." should be used to denote "anabolism-promoting factor".)

Summary and Conclusions

An investigation was carried out in two groups of male subjects to test the relative merits of isoniazid and modified insulin therapy in the physical treatment of neurotic disorders.

In the group of subjects undergoing modified insulin therapy there was a significantly greater increase in weight than was to be found in the group treated with isoniazid. This observation was supported by the subjective response of the patients to treatment and was in agreement with the clinical impressions of those in charge of the investigation.

Reference is made to the possible mode of action of isoniazid in inducing a rapid gain in flesh in tuberculous and non-tuberculous conditions.

It is concluded that isoniazid is unsuitable as a substitute for modified insulin therapy in the treatment of neurotic states.

It is a pleasure to thank Dr. J. S. Harris, Physician-Superintendent, Claybury Hospital, for encouraging me to carry out this investigation on suitable patients in the hospital. My thanks are also due to Dr. Z. A. Leitner, clinical assistant, St. Mary's Hospital, London, for helpful suggestions and advice, and to Dr. W. J. Martin, Statistical Research Unit (Medical Research Council), London School of Hygiene and Tropical Medicine, for advising me on the statistical treatment of the findings.

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RAPIDLY PROGRESSIVE CEREBRAL DEGENERATION (SUBACUTE VASCULAR ENCEPHALOPATHY) WITH MENTAL DISORDER, FOCAL DISTURBANCES, AND MYOCLONIC EPILEPSY

BY

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The two cases which form the subject of this paper presented clinical signs of a subacute degenerative process affecting the cerebral cortex. The mechanism of the pathological changes is obscure but we have, for reasons which will be discussed, formed the opinion that vascular insufficiency is the important factor in their causation. The patients presented clinical features which were on the whole very different from those well recognized as characteristic of cerebrovascular disease, and from such acute manifestations of this disease as hypertensive encephalopathy. Also, in may respects the pathological findings are not those typical of cerebral arteriosclerosis. A few cases have been described in the literature which resemble them, but in none of these has vascular insufficiency been advanced as an explanation of the pathological changes. The relevant literature will therefore be referred to in the discussion of the pathology.

Case Reports

Case 1.—A. C., a housewife aged 66, was admitted to Maida Vale Hospital for Nervous Diseases, under the care of Dr. Dimsdale, on December 8, 1951. She died five weeks later on January 12, 1952.

The patient had been in her usual state of health until 10 weeks before her admission when she became easily fatigued and short of breath, giddy with slight unsteadiness in walking, and subject to double vision at times, particularly in the mornings. She was occasionally forgetful, but no other mental changes were noted until three weeks before admission when she was taken into the Royal Free Hospital for observation. There she quite suddenly became confused, and within a few days was unable to recognize her son except for brief moments. Her condition grew worse; she became restless, noisy, and resistive and was transferred to the Maida Vale Hospital for neurological investigation.

Clinical Examination.—On admission the patient was restless, grimacing, shouting or talking, and was quiet for brief periods only. She seemed at times hallucinated and spoke as if to domestic animals in the room. She was for the most part uncooperative and only occasionally would she obey simple commands. Passive movements were resisted, sometimes with a facial expression of resentment. She appeared quite disorientated for time and place but the delirious state precluded detailed investigation. She was incontinent of urine and faeces. The optic discs were normal but the retinal arteries showed moderate arteriosclerosis. A threat produced a blink reflex from both halves of the visual fields. The pupils were equal and reacted to light; the eye movements appeared to be full. She moved her limbs freely and no motor abnormality was manifest. The deep reflexes were present and symmetrical; the abdominal reflexes were not elicited but both plantar reflexes were flexor. Sensation could not be tested adequately but she appeared to appreciate painful stimuli applied to either side. The blood pressure was 140/90 mm. Hg and the radial arteries were slightly thickened. The heart was not enlarged and no abnormality was found on clinical examination of the chest and abdomen.

The urine, on routine examination, was normal as was the blood count. There was no stippling or abnormality of the erythrocytes although pernicious anaemia had been diagnosed in 1943, since when she had received regular liver injections. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The latter was under normal pressure and contained no abnormal constituents. Radiographs of the skull and ventriculograms were normal.

Progress.—The patient gradually grew worse in hospital and, four days after admission, she no longer spoke coherently although remaining noisy and hyperactive. At this time myoclonic jerks were first observed. They affected mainly the face, eyes and upper limbs but at times involved the whole trunk. They varied in severity from brief twitches not readily seen to large movements affecting an entire limb or the whole trunk. They occurred irregularly at intervals of a second or so for up to half a minute at a time but lessened in frequency when the patient was quiet, and were absent for a time following sedation with barbiturates or paraldehyde. They did not

appear to be influenced by epanutin or by tridione. An electroencephalographic (E.E.G.) examination was first performed at this time and showed a remarkable pattern of high voltage discharges synchronous with myoclonic jerks though occurring also without visible myoclonus. A more detailed analysis of the E.E.G. changes is given below.

At the time of onset of the myoclonic jerking a periodicity in the patient's behaviour was noticed. She would at one time be quiet with the eyes more often closed than open, the arms flexed across the chest, the hands tightly clenched and the feet plantar-flexed. After one to two minutes in this state a single cry would often usher in a noisy, restless period lasting for about 30 seconds during which she flushed, sweated profusely, and breathed more deeply. Coincidentally the myoclonic jerks increased noticeably in frequency. A tachycardia with elevation of the blood pressure up to 200/120 mm. Hg was sometimes, but not always, observed during these excitable periods.

Three weeks after admission the periodicity in behaviour became less marked, the patient being more drowsy with gradual lessening of spontaneous motor activity and utterance of any kind. Myoclonic jerks continued to occur though likewise less frequently ; they could at times be provoked by a pin-prick applied to a limb. Sometimes there occurred brief attacks in which the head and eyes turned upwards and to the right in association with a few clonic jerks of the limbs for two to four seconds. Sometimes these jerks were predominantly right-sided and slight weakness of the right lower face and spasticity of the right arm were noted at this time. No major generalized seizures were observed at any time.

A week before death the patient had become immobile and deeply comatose with bilateral extensor plantar responses. Myoclonic jerks were infrequent. The pulse rate, at first varying, now showed a persistent tachycardia and Cheyne-Stokes respiration occurred intermittently. For two days before death, which took place seven weeks after the onset of the acute mental disturbance, the patient was in a profound coma and unresponsive to any form of stimulus. The myoclonic jerks had ceased.

E.E.G. Observations.—On December 13, five days after admission, the first E.E.G. recording was made (Fig. 1). It showed an unusual pattern of polyphasic high-voltage complexes, synchronous in time in all areas and occurring in long runs at a frequency of about 1 per second with a duration of $\frac{1}{4}$ to $\frac{1}{2}$ second. Separating such runs were periods of lower voltage rhythmical or irregular slow-wave activity, the demarcation between the two patterns being fairly abrupt and clearly apparent. The high voltage complexes varied greatly in shape, having sometimes the appearance of triphasic sharp waves and at others consisting of more sinusoidal activity. The complex recorded from a particular area might vary in

FIG. 1.—Case 1 : initial E.E.G. recording showing a run of polyphasic complexes following upon a period of lower-voltage activity.

shape from moment to moment but sometimes a particular form would recur or would alternate with one of different outline. Often homologous areas of the brain gave rise to complexes closely resembling each other. The amplitude varied considerably from place to place and moment to moment ; sometimes it was highest at the beginning of a run and at other times showed an irregular recruitment. Myoclonic jerks were often observed to coincide with cortical discharges though bearing no apparent relationship to their amplitude or configuration. Many complexes were present, however, without visible myoclonic jerks.

Afferent stimuli of various kinds (Fig. 2) almost invariably effected a temporary inhibition of the cortical discharges, leading either to their cessation or to a clear decrease in amplitude. Repetitive stimuli were not effective in this respect other than at the start of the stimulus period. Within three weeks of admission the E.E.G. had shown a gradual change in that complexes tended at times to be more widely spaced. During involuntary hyperpnoeic periods, however, complexes occurred again at a frequency of 1 per second, continuing so until the hyperpnoea abated and these were not subject to blocking by afferent stimuli. Sometimes complexes were replaced by trains of slow waves lasting one to two seconds with relatively flat periods intervening, and then, after a more pronounced low amplitude phase, the succeeding discharge would again appear as a complex. During the week before death discharges were clearly occurring at greater intervals, and for long periods only bursts of rhythmical slow activity would occur (Fig. 3). High-voltage complexes were, however, still present episodically at the last recording 60 hours before death.

Pathological Findings in Case 1.—At necropsy little of note was found except in the brain. There was minimal atheroma of the aorta and coronary vessels but the radial arteries were tortuous and sclerotic, showing microscopically moderate thickening of the media and some intimal proliferation. Renal arterioles were also thickened to a slight extent. There was no abnormality of the pancreas, adrenals, stomach, or other viscera. Apart from moderate atheroma of the basilar artery the brain presented a normal external appearance and weighed 1,230 g. It was removed entire and after fixation sectioned vertically, material for histological examination being taken from all representative areas.

Cerebral Cortex.—In Nissl preparations the cortical layers were not grossly disorganized but everywhere two pathological changes were evident : first, small areas of status spongiosus and, secondly, some general thinning of the cortical neurons, especially in the deeper layers. The first change was the more prominent and was present in all regions of the cortex examined. It varied greatly in severity from isolated foci to a fairly widespread lesion extending through all layers (Fig. 4). In the frontal cortex only one small focus might be found in any convolution, usually in layers 4 and 5, but at some points

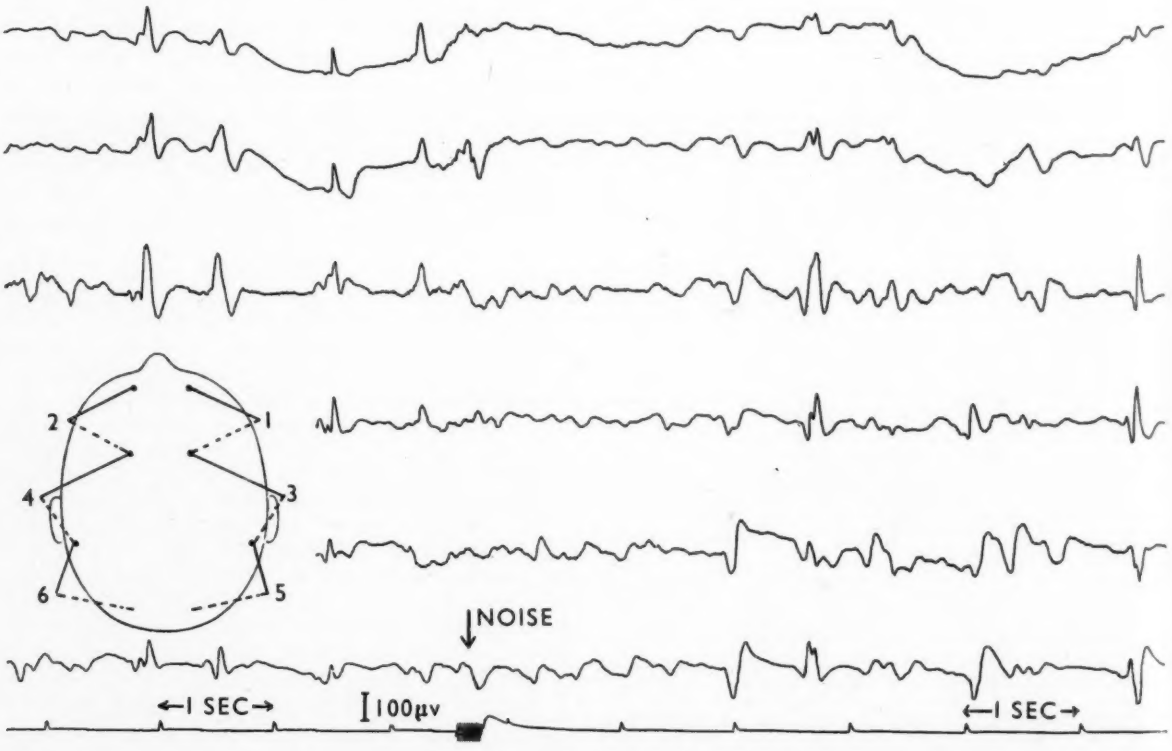

FIG. 2.—Case 1 : sample of E.E.G. showing the inhibitory effect of an acoustic stimulus.

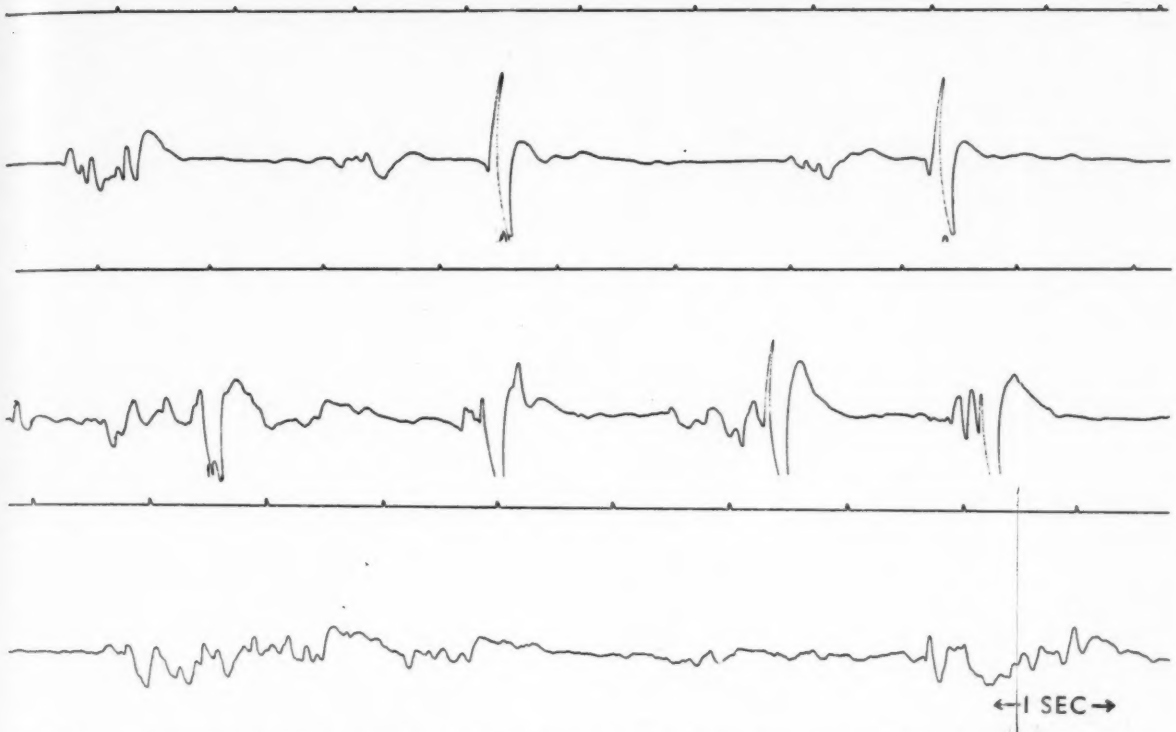

FIG. 3.—Case 1 : recording from brain surface three days before death to show the slower repetition rate of complexes and their replacement at times by trains of slow waves (diphasic sharp-wave in both trace measures/millivolt).

numerous foci of varying size occurred together at the bottom or along the sides of a sulcus.

The condition was on the whole more marked centrally than anteriorly, this being especially so in the upper extent of the superior frontal gyrus where all layers of the cortex were involved. The foci were irregularly oval and elongated in the vertical axis of the cortex ; at some points they coalesced and were surrounded by paling or loss of nerve cells. The post-central gyrus was slightly more affected than the precentral and, still more posteriorly, severe changes were observed in the parietal cortex and superior lip of the Sylvian fissure with predominant involvement of layers 2, 3, and 4. In the temporal lobe the changes were everywhere slight except at the inferior margin of the fissure of Sylvius. No spongiose lesions were seen in Ammon's horn. In the occipital lobe only one or two small isolated lesions were seen in the striate area but in the parastriate region quite large areas of status spongiosus were visible and were especially found at the depths of the sulci. Severe lesions were also found elsewhere in the occipital lobe.

Under high magnification the spongiose lesions appeared as irregular clusters of empty spaces between which strands of ground substance were interwoven. These strands, which stained slightly yellow with van Gieson, contained sometimes isolated neuroglial and oligodendroglial nuclei and, more rarely, faintly staining nerve cells or cell fragments, but otherwise there was complete destruction of parenchymal and ground substance in the area of the lesion. In the tissue adjacent to spongiose areas occasional nerve cells were seen in various stages of dissolution (Fig. 5). Fragments of neurons could be recognized by faintly staining granules and there were also complete cell shadows containing sometimes a swollen and vesicular nucleus. Triangular cell forms were occasionally seen. Though maximal in tissue adjacent to spongiose areas, the neuronal changes were diffusely present in varying degree in all regions of the cortex examined. There was some irregular loss of Betz cells in the motor cortex but, in Ammon's horn, neither in the Sommer's sector nor in the end folium was any gross loss of cells to be seen although some cytolysis of neurons had taken place.

A striking feature was the proliferation of neuroglial cells. These were swollen with a large, faintly granular nucleus and irregular cell body often containing, in the Nissl preparation, dark green granules of considerable size. Neuroglial cells with two or three nuclei were seen. The neuroglial reaction extended into intact cortex as well as being present adjacent to areas of status spongiosus ; it involved all layers but especially the molecular and outer cortical layers (Fig. 6) where it was associated with considerable gliosis. In regions of the cortex where neuronal changes were most severe regressive changes were also present in the neuroglia. There was some microglial proliferation, best seen in the molecular layer, and here it was difficult to discern nerve cells amongst the proliferated glia. Bielschowsky staining

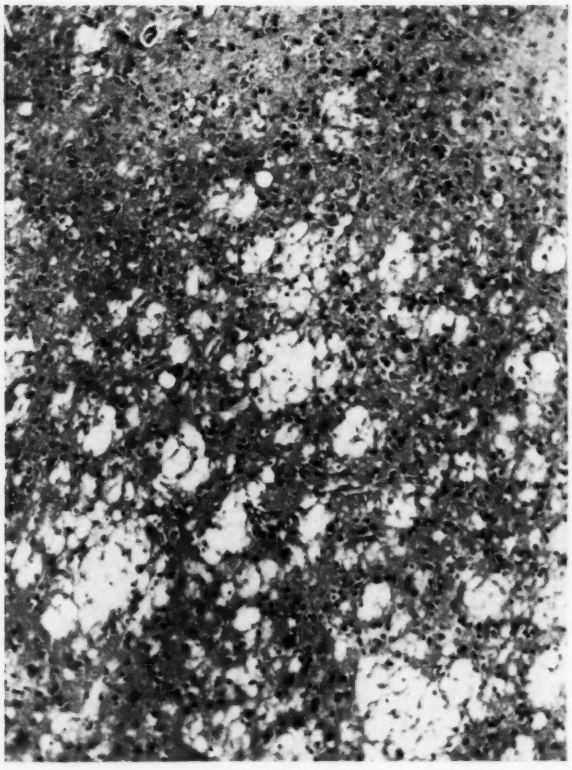

FIG. 4.—Case 1 : central cortex stained with haematoxylin and eosin × 95 to show status spongiosus involving the deeper cortical layers.

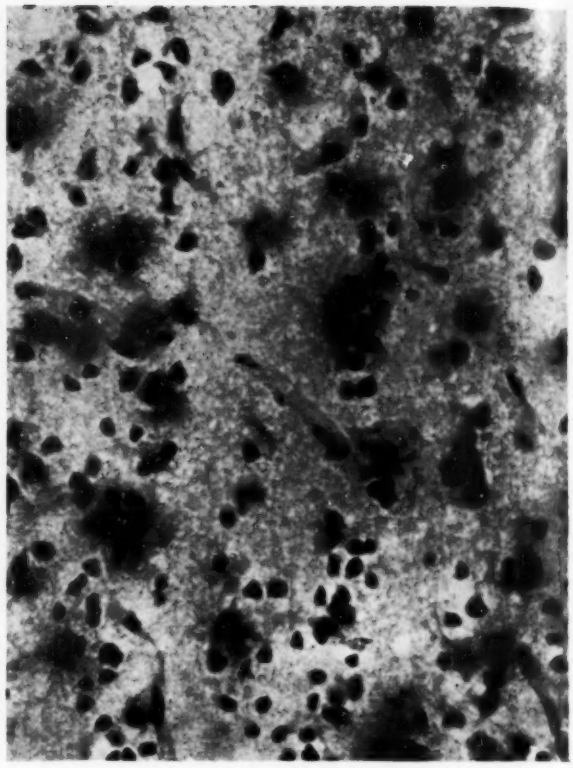

FIG. 5.—Case 1 : frontal cortex stained with Nissl × 280 to show loss and degeneration of neurons, some of which are not easily differentiated from the proliferated neuroglial in the Nissl preparation.

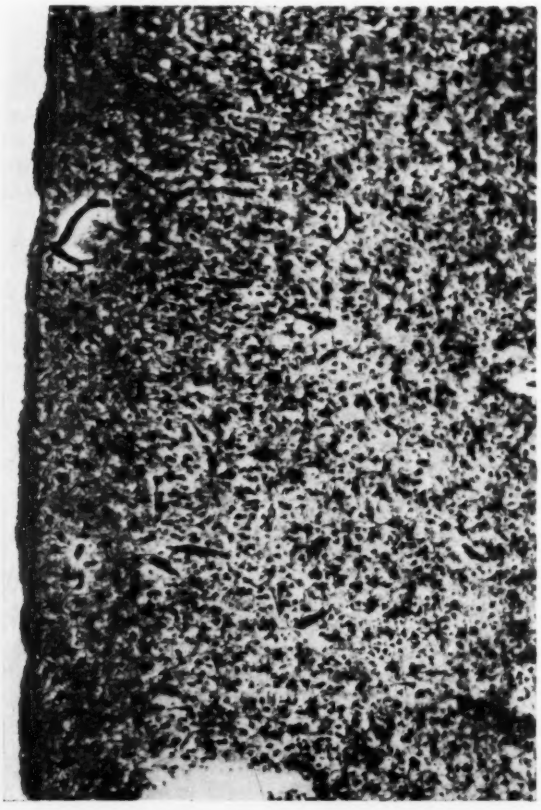

FIG. 6.—Case 1 : frontal cortex stained with Hortega's silver carbonate for astrocytes × 95. The diffuse astroglial reaction is illustrated.

FIG. 7.—Case 1 : section through the basal ganglia nuclei (Heidenhain) showing softenings and *état criblé*.

showed diminution of cell and fibre content of the cortex but this method was not very successful as the brain was not removed until 26 hours after death.

In myelin preparations the status spongiosus, seen with Nissl staining, was very apparent, and radiating fibres were displaced or disrupted. Apart from the spongiose areas, scattered irregularity or interruption of fibres could be seen, and tangential fibres in the molecular layer were sometimes thin and fragmented. The white matter underlying the cortex everywhere stained darkly and no pathological changes were detected.

In the cerebral cortex and subjacent white matter pathological changes in vessels were minimal ; the larger cortical vessels were for the most part intact although there was a good deal of sclerosis of small arterioles, especially in the molecular layer and also to some extent in the white matter where some perivascular dilatation was often observed. Stains for reticulum showed at many points irregular and quite thick reticulum strands or networks spreading along the capillaries, but this was not specifically correlated with the areas of status spongiosus where apparently intact capillaries were also to be seen. There was some leptomeningeal thickening with a moderate amount of hyaline degeneration in surface vessels.

Basal Ganglia.—The most significant pathological change was the occurrence of small softenings, generally oval and a few millimetres in length (Fig. 7). These were present in the basal ganglia, the internal capsule, and the central corpus callosum. They were for the most part complete, showing only a small amount of tissue debris and fat granule cells and surrounded by an irregular zone of neuroglial and fibroblastic proliferation with much new vessel formation. In the caudate nucleus and putamen one or two foci of status spongiosus similar to that present in the cortex were seen and, close to them, some cytolysis of neurons and considerable neuroglial proliferation. In the globus pallidus there was some loss of large cells with overgrowth of neuroglial cells showing large nuclei and green or yellow-green granules in the cytoplasm with the Nissl stain.

Softenings were also apparent in the thalamus, several being located medially close to the ventricular surface. Apart from the softenings the thalamus showed diminution of nerve cells and areas of paling without status spongiosus, and there was also moderate neuroglial and slight microglial overgrowth. A striking feature in the basal ganglia region was the considerable dilatation of perivascular spaces to the extent of producing the appearance of *état criblé*, particularly in the lenticular nucleus, claustrum, and external capsule. In a few of the larger blood vessels, clear fibrous tissue hyperplasia into the enlarged surrounding space had occurred with some lymphocytic infiltration. The majority of spaces, however, especially those surrounding the smaller vessels, were empty. Despite the enlarged perivascular spaces, gross changes in the vessel walls were rare and hyaline degeneration was seen only occasionally in small vessels.

Brain-stem.—In the midbrain, pons, medulla, cerebellum, and upper cervical cord no significant pathological changes were seen apart from a slight outfall of cells in the olivary and dentate nuclei with some neuroglial proliferation. There was a slight loss of Purkinje cells in some of the cerebellar folia with neuroglial overgrowth in the molecular layer as well.

Case 2.—A. L., a male clerk aged 62, was admitted to Maida Vale Hospital on December 19, 1951, under the care of Dr. Dimsdale, and died on January 19, 1952.

There was no history of any significant illness in the past and he had been well until 10 weeks before admission when he noticed slight stiffness of the right arm with a pins-and-needles sensation down its outer aspect, followed within a week by weakness of the limb and unsteadiness on attempted use. Two weeks later, pins and needles were felt in the right leg associated with slight weakness in walking and a tendency to fall to the right. At the same time he noticed difficulty in enunciating words. During the period before entry to hospital weakness of the right side, especially of the arm, slowly progressed and the paraesthesiae were replaced by a constant feeling of numbness.

On admission he was alert, normally orientated, and showed no signs of mental deterioration on systematic testing. He was dysarthric but not dysphasic although right-handed. There was weakness of the right face, arm and leg, most marked in the arm. Spasticity was noticeable only in the arm but the tendon jerks were abnormally brisk in both arm and leg ; the abdominal reflexes were depressed on that side and the right plantar response was extensor. There was loss of postural and vibration sensibility in the arm and, to a lesser degree, in the leg, and two-point discrimination was defective in the right hand. Superficial sensibility was preserved but there was a slight over-reaction to painful stimuli on the right. The visual fields were full and there was no defect of visual attention. A slight nystagmus was present on turning the eyes to the left or upwards. On the left side no weakness or gross sensory loss was found but two-point discrimination was slightly impaired in the left hand. Clinical examination of the heart, lungs, and abdomen revealed no abnormality ; the blood pressure was 120/80 mm. Hg and there was no significant thickening of the peripheral arteries.

Progress.—The patient's condition deteriorated steadily. During the first week dysarthria became more marked and the right hemiplegia more severe, spasticity of the arm giving place to flaccidity ; at times occasional, slow, involuntary movements of the hand took place. The right side became painful to touch or on passive movement. Two weeks after admission spasticity had developed on the left side and at this time myoclonic jerks were first seen. They occurred in episodes lasting several minutes and affected either arm though more prominently the right. The patient remained conscious but slow to respond and grossly dysarthric.

During the two weeks before death paralysis involved all four limbs and the face bilaterally. The patient was drowsy, doubly incontinent, and speechless. Myoclonic jerks of the upper limbs continued, remaining more frequent on the right side Three days before death the

patient would still open his eyes on command but there was by then a complete bilateral flaccid weakness with areflexia. Myoclonic jerking continued though now less frequently. Fever with Cheyne-Stokes respiration, a fall in blood pressure, and peripheral cyanosis supervened just before death.

Left carotid arteriography on December 21 showed a normal arterial and venous pattern but with a 5 mm. shift of the anterior cerebral artery to the right. Air studies a week later did not show this asymmetry, the ventricular system being normal. The cerebrospinal fluid, examined on December 28, 1951, was at a pressure of 170 mm. of water and contained 50 mg. of protein per 100 ml. with 8 lymphocytes per c.mm. (An examination had been performed elsewhere 10 days before with the finding then of a pressure of 100 mm., protein 120 mg. per 100 ml. and no cell increase.) The urine on routine examination was normal, the blood haemoglobin 105%, and the Wassermann reaction negative in blood and cerebrospinal fluid.

E.E.G. Findings.—The E.E.G. recorded on the day of admission showed a low-voltage pattern with irregular runs of slow activity occurring bilaterally. These were most prominent in the frontal region and sometimes more marked on the left side. On the day prior to death bilateral complexes, usually triphasic, were seen (Fig. 8). They would be present for periods lasting 10–15 seconds separated by runs of rather rhythmical slow activity. Sometimes the complexes contained spikes ; they were temporarily blocked by afferent stimuli. No myoclonic jerks were observed during the recording.

Pathological Findings in Case 2.—A post-mortem examination was performed three hours after death. A moderate degree of aortic and coronary atheroma was found but the heart was not enlarged and there was no evidence of degenerative change in the myocardium. The pancreas, kidneys, adrenals, and other viscera were histologically normal.

The brain weighed 1,570 g. but in the occipital and frontal polar regions the cortical surface appeared moderately atrophic with widening of the sulci. Vertical sections revealed slight congestive changes in the white matter but no other gross lesions.

Cerebral Cortex.—The cerebral cortex showed two definite pathological changes, widespread but nowhere of exceptional severity. These were general thinning of the cortical layers, and neuroglial proliferation (Figs. 9 and 10). The latter was most marked in the outer granular and pyramidal layers, giving at some points an appearance of increased cellularity in these regions. Cell loss, on the other hand, was of greatest severity in the deeper layers. Nowhere was there gross disorganization of the cortex and, although sections were taken from many regions, at only one or two points was a minimal and circumscribed cavitation of the ground substance observed. In the deeper layers of the cortex some light-staining remains of degenerated nerve cells were visible at many points ;

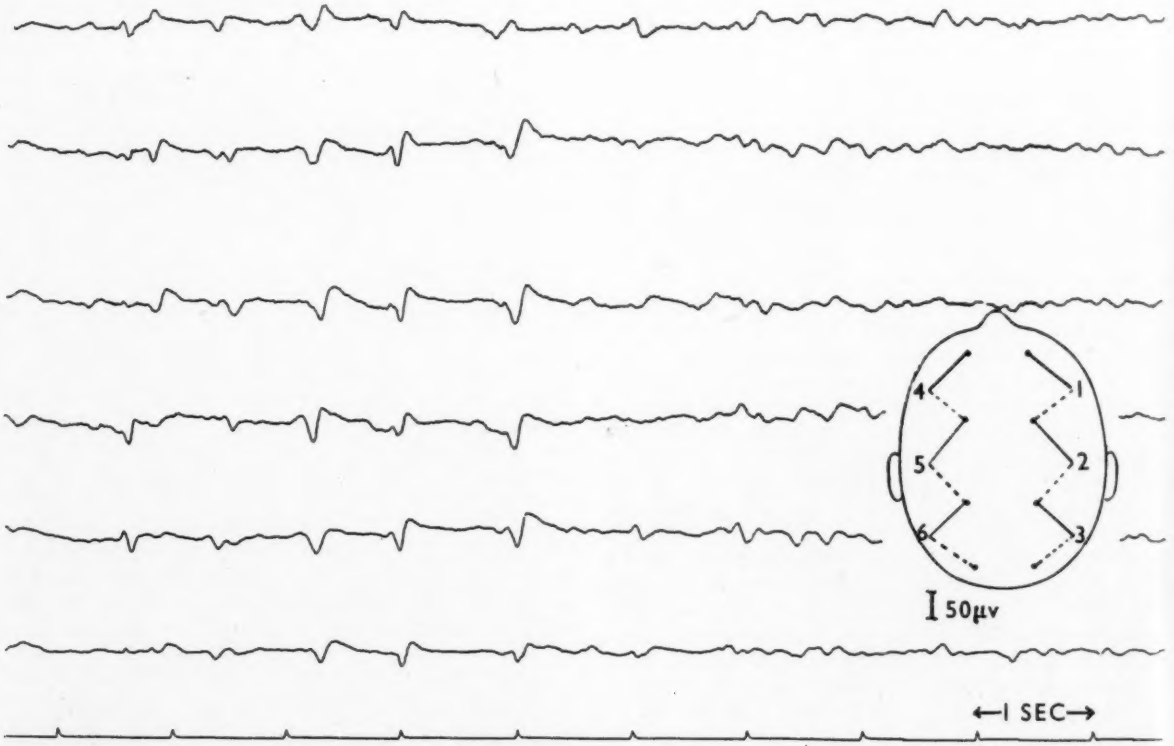

FIG. 8.—Case 2 : E.E.G. recorded on the day before death illustrating the pattern of recurrent discharges separated by periods of lower-voltage waves.

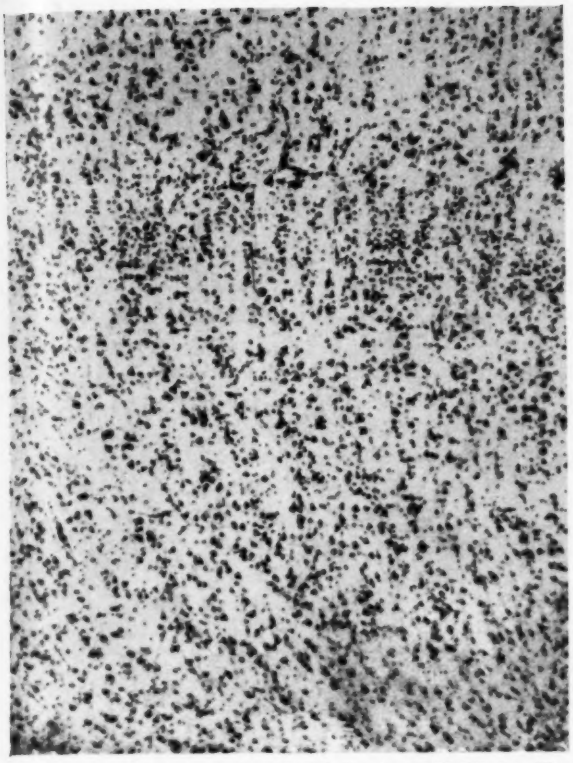

FIG. 9.—Case 2 : cortex in Island of Reil stained with Nissl × 95 to show loss of nerve cells without gross disorganization of the cortical layers.

FIG. 10.—Case 2 : parietal cortex stained with Hortega's silver carbonate for astrocytes × 280 to show neuroglial proliferation in the deeper cortical layers.

FIG. 11.—Case 2 : occipital cortex stained with haematoxylin and eosin × 95 to show slight status spongiosus in the inner layers.

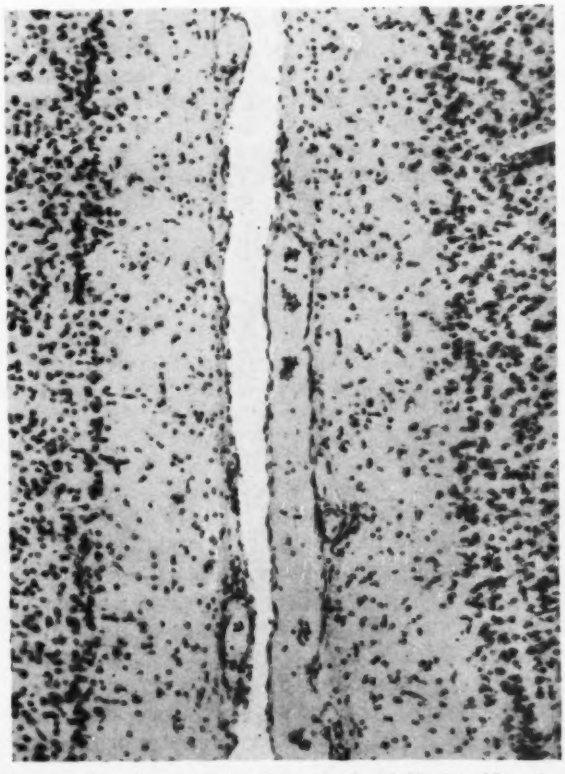

FIG. 12.—Case 2 : occipital cortex stained with Nissl × 95 to show marked neuroglial overgrowth at the junction of the molecular and external granular layers.

at others the nerve cells stained darkly and had shrunken or triangular nuclei, but typical examples of ischaemic or homogenizing cell change were not encountered. Many nerve cells in all layers contained fatty granules of varying number and size.

The proliferated neuroglial cells were enlarged and often the cell body was filled with granules. With Sharlach R these stained red like those in the nerve cells, and with Nissl stain greenish yellow. Often the cells were binucleate. Glial fibre stains revealed intense proliferation of glial fibres under the pia and in the molecular layer but also extending well into the outer cortical layers. There was a slight increase in microglia. Myelin preparations showed no significant change in the white matter nor the cortex.

In the frontal cortex the changes were present in all areas examined and tended to be more marked at the depths of some sulci. Neuroglial proliferation was moderate and fibrous gliosis involved mainly the molecular layer. In the central cortex the gliosis was more marked, with numerous binucleate cells in the outer layers. Some Betz cells had disappeared. In the temporal lobe the region of Ammon's horn was preserved and there was little reactive gliosis or significant thinning of neurons in Sommer's sector and the end folium. In other convolutions of the temporal lobe, however, the typical changes were everywhere present, and particularly so in the lower lip of the Sylvian fissure where considerable fibrous gliosis extended into the second and third layers. Here also, more than elsewhere, a slight tendency to a status spongiosus similar to that in Case 1 was present (Fig. 11).

In the occipital cortex the changes were as severe as in other regions and glial proliferation in the outer layers was especially marked. In one part of the area striata and adjacent parastriate region glial proliferation produced a sharp margin to the junction between the outer granular and molecular layers (Fig. 12).

Changes in the blood vessels were minimal apart from a moderate degree of pericapillary fibrosis, with some hyaline necrosis of the arterioles, especially in the molecular layer of the cortex. Here also, many small vessels in the deeper cortical layers were surrounded by considerably dilated perivascular spaces.

Subcortical Regions.—No significant changes were found in the basal ganglia, brain-stem, cerebellum or upper cervical cord, and there was no degeneration of the pyramidal tracts.

Discussion

E.E.G. Findings.—Although the E.E.G. study of the second case was limited it is clear that, in the later stage of the illness, the abnormalities recorded were similar to those in the first patient. Essentially these consisted of periodically recurring generalized complexes, varying in contour but often with sharp-wave components, and remitting spontaneously or upon afferent stimulation. In the first case myoclonic jerks in different parts of the body were sometimes observed to coincide with the complexes although the occurrence of a jerk bore no apparent relationship to the shape of the discharge, being as often present with one of smooth outline as with one of sharp-wave form. Although this E.E.G. pattern is a very striking one it is not regarded as being in any way pathologically specific.

It is recognized that in subacute encephalitis recurrent complexes are found and that the E.E.G. may be of almost diagnostic distinctiveness (Radermecker, 1949 ; Radermecker and Macken, 1951 ; Cobb and Hill, 1950 ; Martin, Macken, and Hess, 1950). But in lipoidosis likewise (Cobb, Martin, and Pampiglione, 1952) a pattern of recurring discharges of varying shape and periodicity may be seen. Possibly then in these conditions, as well as in the cases here described, the E.E.G. abnormality is of a fundamentally similar nature, the periodic discharges arising as a result of severe, diffuse, cortical pathological change. The individual variations may depend upon the differing effects upon cortical neurons of local lesions and also upon the degree of general disturbance of brain function produced by the disease. In our cases pathological changes in the cortex were widespread and severe and it is easily understood that they could give rise to numerous discharging foci.

We have had the opportunity of observing the effect of 10% metrazol applied to the human cortex at a light plane of anaesthesia and have recorded recurring sharp-wave discharges followed at times by a slow-wave component, whereas, when anaesthesia is deepened, the spike is replaced by a train of slow waves. The similarity between the metrazol effect (previously observed by Johnson and Walker, 1952) and the discharges in our cases is evident, and it is of interest that in the first patient the sharp waves initially present tended to be replaced in the later stages of the illness by somewhat irregular but semi-rhythmic slow waves. It seems logical to infer that the cortical discharge was altered by deepening of the general cerebral disturbance as was the metrazol spike by the deepened anaesthesia and, in fact, pentothal intravenously in dosage of only 0·1 g. was observed to suppress the spike component of the complexes occurring in the earlier stages of the illness.

The unspecific character of these E.E.G. patterns is further shown by the fact that somewhat similar discharges, occurring paroxysmally upon a lower voltage background, may be observed in many juvenile epileptic states, often caused by recognized pathological lesions of varied character. Although this is particularly the case with children, we have observed the phenomenon of recurrent generalized discharges in two adults who failed to improve after craniotomy, in the one case for a pituitary adenoma,

and in the other for a frontal parasagittal meningioma. In both patients the state of consciousness was altered, and it is therefore inferred that, just as pentothal gives rise to periods of activity separated by intervals of low-voltage discharge (suppression-burst activity), so in pathological states the general effects leading to impairment of consciousness may condition the periodicity of the discharges. This may be through alteration of function of subcortical mechanisms, but it is possible that the cortical neurons, with their inherent tendency to rhythmic or periodic discharge, alone are involved.

We have therefore concluded that the E.E.G. pattern in our cases is best interpreted as signifying diffuse cortical discharges made synchronous and periodic by the pathological state of the cortical neurons and their interconnexions. Wesley Watson and Denny-Brown (1953), in discussing the general problem of myoclonic epilepsy occurring in a series of types of degenerative encephalopathies (subacute inclusion body encephalitis, amaurotic family idiocy), emphasize the unspecific character of the E.E.G. changes found in these disease states, changes which they consider as symptomatic of this whole class of disorder.

Pathological Changes.—Three features characterize the pathology in these cases : a widespread cortical degeneration with the formation of areas of status spongiosus, a diffuse neuroglial reaction in the cortex with considerable fibrous gliosis in the first three layers, and focal softenings in the basal ganglia and adjacent white matter. In the second patient changes were found only in the cortex and the status spongiosus formation was minimal, but there can be no doubt about the identity of the pathological process with that in Case 1. In interpreting these changes the presence of small focal softenings in the region of the basal ganglia in Case 1 is especially significant. These relatively recent softenings with irregular margins and surrounded by only a moderate degree of mesenchymal and neuroglial reaction can only be explained on the basis of a circulatory insufficiency in the small arterioles. Clinically and pathologically there is no evidence of any endogenous factor such as hypoglycaemia or of exogenous toxin that could give rise to them.

During clinical investigation of Case 1 several needle punctures of the brain were made, but it is improbable that trauma of this nature could have given rise to the numerous small softenings which were present and, moreover, careful examination of the brain showed that the needle tracks were not in relation to the softenings. A moderate dilatation of perivascular spaces in the region of the basal ganglia, with adventitial proliferation and some lymphocytic infiltration, also points to a primary vascular factor as the cause of the lesions.

It is not, however, easy to explain the mechanism of the vascular insufficiency in that sclerotic changes in the vessels are not so advanced as to make it likely that simple occlusion was the principal factor. A fairly widespread functional disturbance must have taken place to cause numerous softenings all presenting generally similar pathological features at necropsy. In the putamen there existed in the same section a well marked softening alongside a small area of status spongiosus, indicating a tissue reaction of different degree, most probably to the same kind of injury. There seems therefore good reason to regard the widespread cortical lesions as also being vascular in origin. Here again the sclerosis of the arterioles and the pericapillary fibrosis would appear inadequate to cause the lesion directly, while their widespread character is suggestive of a generalized functional disturbance of the circulation.

That a status spongiosus lesion in the cortex can arise on a vascular basis is well attested in the French literature. Lhermitte and Barrelet (1934) and Ameuille, Lhermitte, and Kudelski (1935) have observed it in air embolism, and Alajouanine, Hornet, and Thurel (1936) have described it in the cortex adjacent to haemorrhages in the white matter in three elderly patients, affecting in one instance the fifth and sixth cortical layers and in another the second cortical layer. These authors found, in the close proximity of the status spongiosus to the localized haemorrhage, clear proof of the vascular origin of the lesion which, they consider, may be due to circulatory damage to nerve cells, ground substance, or neuroglia with possibly hydration of the tissues. Status spongiosus has been a common finding in the brain of general paralytics especially in those with marked focal symptoms and convulsions, and here again Merritt and Springlova (1932), after a detailed study of the problem, conclude that the status spongiosus lesion is produced by the combination of a functional disturbance of the cerebral circulation with the inflammatory process. Bielschowsky (1919) discussing the same problem (status spongiosus in general paralysis of the insane) considered altered permeability of the cortical vessels leading to fluid accumulation in the tissues an important factor.

According to Spielmeyer (1922) a status spongiosus is indicative of an acute softening of the tissue (to be distinguished from the more usual vascular softening) in which the protoplasmic glia of the cortex and basal ganglia fails or is incapable of reacting to repair the defect. This concept may well be valid for

the purely degenerative lesions of this type but it is probable that status spongiosus also occurs on a basis of vascular insufficiency, not necessarily complete but of a critical intensity, and associated with fluid exudation and impaired absorption. How this has been brought about in the cases described in this paper—where not only extensive spongiose lesions (especially in Case 1) were present, but also less intense tissue damage with focal cell loss and a widespread glial reaction approaching in form to *gemästete* glia—is the primary problem presented by this study. It is doubtful if it can be solved histopathologically. A functional impairment of cerebral circulation has been assumed and there is some clinical evidence to support this view in that, in the second case, the right-sided hemiplegia in the early stage of the illness was associated with some oedema of the left cerebral hemisphere as shown by the displacement of the anterior cerebral artery in the arteriogram. This suggests that the cerebral lesions had possibly resulted from vascular stasis and increased permeability of the vessels. Both patients were elderly with some degree of arteriosclerosis and it is probable that the defect is primarily a vascular one, although the possibility of some chemical or metabolic factor of endocrine or other origin acting on the vessels has to be borne in mind. For its existence, however, no clinical or pathological evidence is to hand. It seems very probable that further light on the problem may only be obtained by measuring the cerebral blood flow, and by a study of the reaction of cerebral vessels, in other similar cases, to those chemical and hormonal factors that are known to influence them.

The condition appears to be rare and we have not discovered in the literature comparable cases in which a vascular aetiology was thought to exist. Hallervorden (1930), however, under the title of " Peculiar and Non-classifiable Conditions ", has described what appears to be a similar type of case. A 60-year-old woman died of erysipelas after an illness lasting three to four months characterized by mental disorder, hemianopia to the right, ideational apraxia, alexia, and excitability with perseveration in the utterance of meaningless words. Pathologically a fine status spongiosus, greatest in layers 2 and 4, was present over the whole cortex and affecting especially the posterior regions with nerve cell degeneration and neuroglial reaction in general similar to that present in the cases in this paper. Hallervorden regarded the condition as a purely degenerative process affecting the cerebral cortex. Fischer (1911) described a similar type of case in a 70-year-old man in whom the duration of symptoms was also four months. A sudden onset with focal symptoms pointing to the left temporal lobe had occurred in this case which showed, pathologically, focal atrophy in the left temporal region and a status spongiosus throughout the rest of the cortex.

Under the title " Concerning a Peculiar Organic Disease of the Presenium ", Heidenhain (1928) describes three cases which are all similar pathologically to those described in this paper. In the first patient aged 55 and in the second aged 53, both of whom died after an illness of 16 to 20 weeks, the prominent symptoms were cortical visual disturbance leading to blindness and profound mental changes characterized by excitability, clouding of consciousness, and disorientation. Gross palsies of one or other limb were not present but spasms of the whole musculature took place repeatedly.

In the third case the patient had been ill for a number of years but the terminal illness, characterized by rapid mental deterioration and epilepsy, may well have been a subacute encephalopathy of the type under discussion. Heidenhain regarded his cases as arising on a degenerative basis although he differentiates them pathologically from the degeneration which is found in Jakob Creutzfeld's syndrome and from other degenerative and inflammatory conditions. On account of the normality of the vessels he does not consider a vascular basis as possible, although he adopts the view that the status spongiosus is produced by severe exudation into the tissue spaces, as the myelin sheaths are clearly displaced by this particular lesion in some places. This view, if correct, points to some disturbance of circulatory function so that some vascular insufficiency as a cause of the nerve cell degeneration and neuroglial reaction is not an altogether impossible explanation of Heidenhain's cases.

There can be little doubt that these cases from the literature are similar pathologically to those described in this paper. We have considered a disorder of vascular function occurring in ageing and somewhat sclerotic cerebral vessels to be the most probable cause, but recognize that further study of the condition, clinically and pathologically, will be necessary to establish this, to elucidate further the mechanism of the vascular failure, and to determine whether or not altered capillary permeability is also a factor. Hallervorden (1930) referred to another case in the German literature in which an atrophic condition, progressive over some years, showed at necropsy a status spongiosus lesion of the cortex adjacent to a large atrophic area. He made the suggestion that a similar type of pathological process of more gradual development may underlie some of the rare and obscure focal atrophies in

younger subjects. This suggestion appears to us well founded and points to the need for further histological study of biopsy material in such cases.

Concluding Remarks

The two patients whose case histories have been discussed in this paper, and the five described in the literature, appear to have suffered from a similar type of subacute encephalopathy. On the clinical side the analogous features are vague prodromal symptoms leading to a focal cerebral disorder such as hemiparesis, hemianopia, blindness, apraxia, or alexia associated with severe mental disturbance. Myoclonic epilepsy is a striking feature of the cases but may, in some instances, be absent unless we are incorrect in including in this type of encephalopathy the patient described in Hallervorden's article. We have put forward the view that there is at least a prima facie case for regarding the pathological changes as due to abnormal functioning of the cerebral vessels and consequent impaired nutrition of the cerebral cortex. On this basis it is proposed to refer to the cases as subacute vascular encephalopathy, a title which will distinguish them on the one hand from hypertensive encephalopathy, and on the other from the more slowly progressive states resulting from cerebral arteriosclerosis. If the vascular origin of the condition is eventually established then its clinical and pathological basis may eventually be considerably widened to include such cases of subacute encephalopathy as those described as vascular in origin by Alajouanine and van Bogaert (1950), cases somewhat different clinically and with more widespread pathological changes.

One final point worthy of empahasis is that the E.E.G. abnormalities, although in no way pathologically specific, may nevertheless prove helpful in diagnosis because of their rarity in adult life and because they indicate acute and generalized cortical disturbance. In a review of 100 cases of chronic cerebrovascular disease a similar pattern was not seen nor, to our knowledge, has it been described in degenerative conditions in this age group.

Summary

A clinical, electroencephalographic, and pathological description is given of two cases of a rapidly fatal illness in late adult life in which myoclonic epilepsy and progressive impairment of consciousness were striking features. The E.E.G. showed an unusual pattern of recurrent sharp-wave discharges over both hemispheres, and its significance in relation to the histological findings is discussed. In both patients death ensued within 15 weeks of the onset of the illness. In one there was a marked status spongiosus of the cortex, a general loss of cortical neurons, marked glial overgrowth, and numerous acute softenings in the basal ganglia. In the other, similar but less marked cortical changes were present. A vascular aetiology is postulated for the cerebral lesions, and for rapidly progressive cases of this type the name subacute vascular encephalopathy is suggested. Cases in the literature which are possibly similar are briefly discussed.

It is a pleasure to thank Dr. W. H. McMenemey for his help and advice in the preparation of this paper. We are also indebted to Mr. and Mrs. Gordon Cox, of the Pathological Department, and to Mr. Roberts and Miss Walker, of the E.E.G. Department, for their technical assistance. We are also grateful to Dr. Helen Dimsdale for permission to publish her cases.

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BOOK REVIEWS

Nervous Transmission. By Ichiji Tasaki. (Pp. 164 ; 77 figures. 55*s*.) Springfield, Illinois : C. C. Thomas ; Oxford : Blackwell Scientific Publications. 1953.

Twenty years ago physiologists of the Japanese school, and foremost among them I. Tasaki, began to experiment with single myelinated nerve fibres partly separated by dissection from toads' nerve trunks. Their working hypothesis was the view, first put forward by R. S. Lillie, that in such fibres the impulse jumps from one node of Ranvier to the next, the resting nodes being serially excited by outwardly flowing electric currents generated by the active nodes upstream. Since Huxley's and Stämpfli's well-known experiments, saltatory transmission has been generally accepted as a fact. Tasaki's monograph is important in that it is the first compact statement of the strong and pioneering Japanese evidence to be set before British and American readers.

The first discovery was that narcotics retard and eventually block transmission by a selective action on the nodes, and that the threshold for electrical stimulation with a micro-electrode is highest at the middle of the internodes and lowest at the nodes.

Nerves were dissected so as to expose a length of single fibre containing two or more nodes. These nodes were placed in pools of Ringer's solution, each mounted on a glass plate separated from neighbouring plates by " bridge-insulators " of air or paraffin oil. Across these insulating gaps lay the myelin-sheathed internodes. Current generated in the preparation therefore flowed along the axis cylinders from node to node, and traversed the nodal plasma membranes, in a circuit completed by the electrical recording system which linked the pools externally. Stimulating currents could be sent round the same circuit in either direction, and measured by the same recording apparatus.

The reactions of a single node of Ranvier were isolated by inactivating its neighbours by adding cocaine to their pools. Such an isolated node is excited by currents flowing outwards through it. Excitation is signalled by an inward surge of action current. This current is five to seven times larger than the threshold-stimulating current. That excitation is due to current flowing across the nodal membrane, and not to current flowing along the axis cylinder, is proved by sending two currents towards a single node from either side. Their sum, i.e., the resultant outward current through the node, has a constant threshold value ; stimulation is independent of their separate magnitudes and of the direction of axial flow.

When the nerve-trunk is stimulated upstream of the dissected region, an impulse passes along the single fibre and causes a twitch in the muscle attached to the nerve distally. Each node shows, first, an outward flow of current generated by previous nodes. This current is five times stronger than that needed to stimulate the node. The node reacts by an inwardly directed action current. And after the impulse has passed beyond it the node shows an outward current due to the activity of later nodes. The stimulating outward current is a little smaller than the action current of the previous node, for it is attenuated by the leaky myelin sheath. This leakage is exaggerated by saponin, which, since weaker stimulating currents excite the nodes with a longer latency, increases the internodal transmission time.

The effect of narcotics on transmission is of the greatest interest. The impulse can jump beyond one or even two locally inactivated nodes. If, on the other hand, the nerve is subjected to progressive narcosis, the threshold of each node is raised and the action current reduced, therefore the latency of nodal excitation is increased, and the conduction velocity of the impulse is correspondingly reduced. The impulse is blocked at the stage when the reduced action-current of one node falls short of the raised threshold of the next. Yet appropriate stimulation still elicits from any node, in all-or-nothing fashion, an action-current of nearly half the normal size. Similar changes in nodal action-current and threshold are brought about by refractoriness after the passage of an impulse, with similar consequences for impulse-transmission.

The book is remarkable for its brilliant analysis of the electrical records. Those showing the effect on transmission of electrical polarization of two adjacent nodes by ascending and descending currents are outstanding in this regard. The argument is throughout clearer and more rigorous than any summary of it can convey.

Cerebral Mechanisms in Behaviour—The Hixon Symposium. Edited by Lloyd A. Jeffress. (Pp. xiv + 311 ; illustrated. 52*s*.) London : Chapman and Hall. 1951.

The Hixon symposium met in 1948, and this book, the report of its deliberations, was published in 1951. When it met, the influence of cybernetics was still fresh and this is reflected in much of the discussion. As a result it occasionally wears an air of the faded enthusiasms of yesteryear. A mathematician, von Neumann, opens the book with a paper on the general and logical theory of automata. He speaks of automata which in theory should be able not only to correct their errors but also to reproduce themselves and construct others.

W. S. McCulloch then discusses the possible similarities between the functioning of computing machines and cerebral activity, especially learning and memory. However, he seems to doubt if such mechanisms will explain all the activities of the human brain, since he concludes " The joy of creating ideals . . . robots have it not." Presumably, if one follows von Neumann, they miss the joy rather than the creating : though this is not quite clear. A paper by Lorente de No had to be omitted, though one important point he made, which emerged in discussion, was that there may well be many different types of nerve cell rather than one single kind as is at present usually assumed. K. S. Lashley then discusses the time factor in central nervous system function. The problem may be summarized in one of his own sentences " the architect designing a house . . . presents a problem of sequences of action which cannot be explained in terms of successions of external stimuli ". This excellent paper and its discussion are likely to be of special interest to the neurologist or physiologist interested in the wider aspects of neural function. Kohler describes the changes in behaviour observed in monkeys with occipital and temporal lobe lesions and Nielsen mentions clinical cases. Kohler speaks of the *gestalt* approach to perception and his own contributions to this theory. Finally Halstead discusses brain and intelligence with reference to local brain lesion, especially of the frontal lobes : and Brosin considers the symposium's bearing on clinical practice in psychiatry.

In general the discussion following each paper benefits greatly by having experts in varying fields taking part. A great many findings of neurological interest emerge incidentally in this way : and much imaginative speculation—an important ingredient for scientific advance—is given rein. Although the impression is created at times that all the problems of cerebral function can be solved, even though with difficulty, by a mechanistic analysis, this is due largely to the language used and in fact there are plenty of instances which suggest that even the discussants of the Hixon symposium see realms of mental life still unsolved in space and time. Certainly the book can open new horizons for the receptive mind in clinical and pre-clinical neurology.

Progress in Clinical Psychology. Edited by Daniel Brower and Lawrence Abt., Vol. I, Sections 1 and 2 (Pp. 564. 37*s.* 6*d.*) New York : Grune & Stratton ; London : George Allen & Unwin. 1952.

This first volume in an intended biennial series seeks to review advances in clinical psychological practice and research between the years 1946 and 1951. Its 42 chapters (with a total of 2,797 references) cover a range from the better known intelligence scales, through multitudinous personality measures, to more applied branches such as vocation guidance, delinquency, and addiction. Every chapter is written by a specialist in that field, few of whom survey more than the current American literature. Working familiarity with the test procedures and with statistical terminology is assumed.

Most of the studies described in this volume relate either to intercorrelation or to validation of the many tests now available. While some of the authors are well aware that most tests lack adequate validation, the book as a whole reflects the bias in America towards the use of projective techniques, and their interpretation in terms of uncritically accepted psycho-analytic concepts.

The reader in this country should be reminded that the mandate of the clinical psychologist in the National Health Service does not extend to therapy and " counselling ", to which a section of the book is devoted.

The volumes in this series should make a useful addition to reference libraries, but will hardly serve as an introduction to the techniques of psychological testing.

Psychiatric Dictionary. By Leland E. Hinsie and Jacob Shatzky. (Pp. 781, including Supplement. 120*s.*). Oxford University Press (London : Geoffrey Cumberlege). 1953.

In producing a dictionary of terms used in some special field of knowledge it is necessary to steer a middle course between the inclusion of common words whose everyday meaning suffers no real change and can be readily understood in their special context, and the inclusion of neologisms of very limited and probably transient usage. This work suffers from both forms of inclusiveness. " Adventurousness ", for example, is defined much as in any standard dictionary (except for the rather verbose and laboured exemplification), while " triskaidekaphobia " (fear of the number 13) almost arouses the suspicion of having been coined in order to appear in this volume ! The dictionary fails in another respect which is perhaps unavoidable at the present stage of development in psychiatry. Its definitions of important terms in some special branches such as psychoanalysis tend to be inadequate, because current development has changed, or is changing, usage.

Amongst smaller points of criticism, a long paragraph devoted to definition and exemplification of " Golem ", a figure from Jewish mythology, seems misplaced in a psychiatric dictionary. The inclusion of 12 separate words with the prefix " pseudo- " seems a waste of space, since the prefixed words are themselves adequately defined. Similarly, separate definition of the adjectival form and its variants of an adequately defined noun seems unnecessary. This of course assumes that the dictionary is intended for a reader of average intelligence. It is, however, difficult to see what public it can in fact serve, except those who wish to imply a knowledge they do not possess by decking their conversation with technical neologisms. The fact that a second edition with a supplement has been called for 13 years after the first suggests that such a public is growing. The price of 120*s.* will limit the sale of the book in this country.

The National Hospital, Queen Square, 1860-1948. By Gordon Holmes. (Pp. 98 ; illustrated. 10*s.* 6*d.*) Edinburgh : E. and S. Livingstone. 1954.

" The National Hospital for the Relief and Cure of the Paralysed and Epileptic " came into being in 1860 at first

with only eight beds for women. This adventurous new development owed its origin to the efforts of a Miss Johanna Chandler, a middle-aged woman in poor health, who was shocked by the absence of charities to provide for the paralysed, and " decided to devote her life to supply this great want ". This worthy ambition happily coincided before long with a flood of advancing knowledge with regard to the nervous system which attracted some of the best brains in medicine, as a rapidly progressing specialty always should.

In this short book the author describes the dramatic growth of the hospital and the striking personalities of many famous physicians and surgeons who contributed to the unique position of " Queen Square " in neurological history.

Miss Johanna Chandler could hardly have anticipated that her dream would emerge into such a highly scientific organization for diagnosis, treatment, and research, but perhaps she might even to-day feel that there is still more to be done towards relieving the suffering of the paralysed. Those who have worked in the National will wish to have a copy of this interesting book.

How to Use a Medical Library. By L. T. Morton. Second edition. (Pp. 44. 5*s*.) London : Heinemann. 1953.

This little book sets out to help the practitioner or research worker to find what he is looking for in a medical library—a task which he often finds beyond him —and it more than adequately achieves this aim. Those who have been mystified by the formidable array of index cards which is the *vade mecum* of any library will find such mysteries elucidated in the chapter on catalogues ; and there is, too, a useful chapter giving the various sources of information available for readers who are not fully acquainted with the existing literature on their subject.

In a handbook of this sort it is perhaps questionable whether the historical details given in the newly-added section on abstracting services add more to its value than the full list of these given in the first edition, but there can be no doubt about the usefulness of the list of principal libraries in Britain which gives not only their size and scope but also their accessibility to the would-be reader.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Viruserkrankungen des Menschen. Ein Lehrbuch der Klinik, Epidemiologie und Ätiologie der Menschlichen Virosen. By W. D. Germer. (Pp. 190 ; 47 figures. DM. 30.–) Stuttgart : Georg Thieme Verlag. 1954.

Die Bedeutung des Blutchemismus. By E. Leupold. (Pp. 207 ; 102 figures, 116 tables. DM. 48.–) Stuttgart : Georg Thieme Verlag. 1954.

Memorie Scientifiche dedicate a vito Maria Buscaino nel XXV Anno del suo insegnamento. (Pp. 543 ; illustrated.) Naples : Clinica della Malattie del Sistema Nervoso dell'Universita di Napoli. 1953.

Physiologie des Lobes Frontaux et du Cervelet. Étude Expérimentale et Clinique. By John F. Fulton. (Pp. 158 ; 48 figures. Fr. frs. 1,000.–) Paris : Masson et Cie. 1953.

Die Zentralnervösen Wirkungen von Heilittelmn. By E. Rothlin. (Pp. 39 ; 7 figures. DM. 2.40.) Stuttgart : Georg Thieme Verlag. 1954.

Transactions of the Ophthalmological Society of the United Kingdom, Vol. LXXIII, Session 1953. London : J. & A. Churchill. 1953.

Manic-Depressive Disease. By John D. Campbell. (Pp. 403. 55*s*.) Philadelphia : J. B. Lippincott. 1953.

Peripheral Nerve Injuries : Principles of Diagnosis. 2nd ed. By Webb Haymaker and Barnes Woodhall. (Pp. xv + 333 ; 272 figures. 35*s*.) Philadelphia and London : W. B. Saunders Company. 1953.

Modern Clinical Psychiatry. 4th ed. (Pp. viii + 609. 35*s*.) Philadelphia and London : W. B. Saunders Company. 1953.

Diagnostica Psichiatrica (Parte Generale). By V. M. Buscaino. (Pp. xii + 290 ; 35 figures.) Naples : Casa Editrice Libraria V. Idelson. 1954.

Heredity, Health, and Mental Disorder. By Franz Josef Kallmann ; Foreword by Nolan D. C. Lewis. (Pp. 315 ; 89 figures, 20 tables. 42*s*.) New York : W. W. Norton & Company ; London : Chapman & Hall. 1953.

Die Halswirbelsäule Pathologie und Klinik. By Gerhard Exner ; Foreword by Georg Hohmann. (Pp. 140 ; 42 figures. DM. 21.60.) Stuttgart : Georg Thieme Verlag. 1954.

Endocrine Disorders in Childhood and Adolescence. 2nd ed. By H. S. Le Marquand and F. H. W. Tozer ; Physiology section re-written by W. J. Tindall. (Pp. xiii + 332 ; 90 figures. 32*s*. 6*d*.) London : English Universities Press. 1954.

The Psychiatrist : His Training and Development. Report of the 1952 Conference on Psychiatric Education held at Cornell University, Ithaca, New York, June 19–25, 1952. (Pp. viii + 214.) Washington: American Psychiatric Association. 1953.

The Integration of Behaviour : Vol. I—Basic Postulates ; Vol. II—The Integration Process in Dreams. By Thomas M. French. (Pp. xi + 272 ; xi + 367. 37*s*. 6*d*. and 49*s*. respectively.) London : Cambridge University Press. 1954.

Verstehen und Einfühlen. Gesammelte Schriften. By H. W. Gruhle. (Pp. vi + 458. DM. 29.60.) Berlin : Springer-Verlag. 1953.

Gehirn und Auge. By Robert Bing and Rowland Brückner. (Pp. 248. Sw. frs. 14.–.) Basle : Benno Schwabe. 1954.